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DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1975 through June 30, 1976

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NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES -- DR. JOE R. HELD, DIRECTOR

Report of Program Activities
July 1, 1975, through June 30, 1976

A. Objectives

The Division of Research Services supports intramural biomedical research being conducted by the various Bureaus, Institutes, and Divisions (BIDs) of the NIH. The staff of professional and technical personnel concentrates on meeting the unique requirements that develop as research investigators' plans and experiments evolve. They collaborate with laboratory scientists and administrators, and also carry out independent research to provide needed products and services. Division programs are organized into five functional areas: Biomedical Engineering and Instrumentation, Environmental Health and Safety, Library, Medical Arts and Photography, and Veterinary Resources.

B. Current Programs

Division programs offer a broad range of products and services. They include:

1. The application of engineering principles and techniques to the solution of biomedical problems.
2. The design, fabrication, and maintenance of special research instruments.
3. Environmental surveillance to detect and eliminate conditions adverse to conducting high quality research or hazardous to patients, employees, or the community.
4. Surveillance of biohazards, control of radioactive materials and maintenance of health and safety programs.
5. Library and bibliographic services.
6. Foreign language translation.
7. Still photography and motion picture production.
8. Graphic arts services and exhibits design.
9. Medical illustration and model making.
10. Animal production, procurement, conditioning and holding.
11. Animal health services.
12. Experimental surgery and related activities.
13. The production of tissue cultures, microbiologic medias and animal biologics.
14. Central processing and sterile preparation of laboratory glassware.

C. Program Progress and Accomplishments

1. Biomedical Engineering and Instrumentation

There was an increasing number of collaborative projects focused on observing describing, and analyzing biological systems *in vitro* or *in vivo*. The organizational level of these systems ranged from the biochemical through the cellular or tissue to the whole body.

At the biochemical level, developments included: a pulsed Fourier transform nuclear magnetic resonance spectrometer usable for several nuclei; a thermal titration apparatus capable of measuring heats of reaction associated with chemical reactions of protein such as acid/base titration; and an improvement of atomic absorption spectrophotometry to permit assay of trace amounts of endogenous or exogenous metals in biological specimens.

At the level of the cell or tissue *in vitro*, several techniques were investigated and instruments developed. The optical-thermal properties of liquid crystals were examined for relevance to temperature measurements on the size scale of a single cell. A capillary membrane-based tissue culture unit, developed in an earlier collaborative project, was instrumented and analyzed to permit rigorous metabolic studies on mammalian cells grown to tissue-like density. An integrated isometric myograph and optical system is making possible measurements of hypertrophy and phosphorylation of muscle preparations and other tissue preparations, including embryological systems.

Principles of chemical reaction engineering were applied to the distribution of drugs, environmental contaminants, and endogenous metabolites in animals and man. This leads to more quantitative specification of anti-cancer drug therapy and provides operational bases for extrapolation between species. The feasibility of fluorescence spectroscopy at the microscopic level *in vivo* was established by a device employing miniature fiber optic probes.

A clearer understanding of the interaction among design features, materials properties, and the biological environment has emerged from studies of sucessful heart assist devices, ventricular-aortic by-passes, and composite heart valves. Novel design concepts were explored to develop a miniature catheter capable of insertion into small convoluted blood vessels. The wall shear stress distribution has been measured in a model of a canine aorta by an electrochemical technique, and fluid dynamic phenomena correlated with the location of atherosclerotic lesions.

Various steps, including contracting for some support activities, were taken to improve technical services for research support.

2. Environmental Health and Safety Program

a. Office of the Associate Director for Environmental Health and Safety

Reorganization of the Environmental Health and Safety Program to bring all elements of the program under central management was completed in January 1976. The program now functions through two operating units: the Environmental Safety Branch and the Radiation Safety Branch. Under the reorganization, the Environmental Safety Branch was expanded from two to four units. It now consists of the Environmental and Industrial Hygiene Section, Biological Control Section, Occupational Safety and Health Activities Section, and the Media and Glassware Section, which was transferred from the Veterinary

Resources Branch. All functions of the original Environmental Services Branch and the former Safety Management Program, DRS, have been incorporated in the Branch's activities.

During the year, a periodic medical surveillance program was begun for employees exposed to specific hazards. Activities required by the National Environmental Policy Act and other Federal regulations were intensified to maintain NIH compliance. Training materials, including films and other visual aids, were developed, distributed, and presented to personnel. An information system was established on environmental health and safety for NIH employees, including an emergency hazard warning system. Special investigations of laboratory incidents were carried out and the findings disseminated throughout the biomedical research community with recommendations for prevention.

b. Environmental Safety Branch

The Branch assisted in the planning of several new facilities particularly in relation to solid waste handling procedures, laboratory safety, and adherence to required environmental health and safety design standards.

The staff worked with NIH and DHEW developing guidance for intramural and extramural laboratories using DNA recombinant molecules, hazardous biological materials, and chemical carcinogens.

Direct assistance was provided to 39 laboratories outside of NIH on various matters concerning biological safety. The NIH Biohazards Safety Guide was distributed to 2,100 investigators; 1,100 copies were sent to laboratories outside of NIH. Five hundred copies of the Self-Evaluation Guide for the Hospital Environment also were distributed.

An accident ADP reporting system was integrated with the DHEW ADP system. This system eliminates the need for trans-shipment of accident reports and subsequent coding by the Department. It also provides for NIH study of accident and injury causes.

A major contribution to the nation's biological research effort culminated in development of performance standards for Class II biological safety cabinets through the National Sanitation Foundation. The Branch collaborated with the Foundation to establish a testing laboratory which will provide services for certification of biological safety cabinets and related equipment on a nationwide scale. The test laboratory is expected to be in operation by the end of calendar year 1976.

The NIH chemical waste disposal plant was reconstructed and revised operational procedures were developed. Chemical carcinogen waste disposal procedures were established in an NIH standard to help improve this type of waste handling. The Environmental Protection Agency established new effluent criteria for the liquid waste treatment at the NIH Animal Center in Poolesville, Md. Staff assisted plant operators in new operational procedures and established a new sampling program to meet EPA requirements. The solid waste system underwent major changes with conversion of the NIH collection system to paper bags and cardboard carton waste containers, to make it compatible with a new NIH incinerator and a future county medical-pathological incinerator.

c. Radiation Safety Branch

Nuclear Regulatory Commission representatives inspected three licensed activities in February 1976 and their findings indicated a significant improvement in NIH radiation safety practices compared to the 1972 inspection. Improvements in laboratory safety practices and the passage of more than a year without a reportable radiation incident were attributed in large measure to increased emphasis on training and surveillance instigated in 1972. However, several areas of concern still remain, including a need for more effective monitoring of radioactive effluent from various buildings; routine review and renewal of investigators' authorizations; increased level of training, particularly retraining authorized users and x-ray technicians; improved security for byproduct materials; more frequent bioassays of radiation workers; and continuing efforts to maintain personnel exposures as low as reasonably achievable. Difficulty has also been experienced in providing the desired quality of service to the research laboratories, particularly in regard to radioactive waste disposal, because of limited program resources. The volume of such waste has risen approximately 30 percent in each of the past several years and there has not been an accompanying increase in manpower to handle it. Funds have been secured and plans are being put into effect to pick up, process, and dispose of the waste under a service contract.

3. Library Branch

Preparations continued toward installation of the Automated Circulation Control System which will provide more effective service and control of books and journals loaned to NIH Staff. Conversion of bibliographic book and NIH user records into computer data files has been completed.

The Library staff completed a Scope and Coverage Policy for the NIH Library and it became effective as a guide for the selection of literature.

New terminals were installed to speed bibliographic retrieval services for researchers via MEDLINE (Medical Literature Analysis and Retrieval System On-Line) and the new TOXLINE (Toxicology Information On-Line) data bases at the National Library of Medicine.

The Library's literature in non-print form has been organized in a central area and a modest number of audiotapes and videocasettes have been acquired.

4. Medical Arts and Photography Branch

Demand for MAPB services increased approximately 10 percent in FY 1976. The larger workload was met by a corresponding increase in contracted services. Delivery of finished artwork was accelerated and the delivery of normal photographic service was reduced from seven to five work days. Graphic standards for statistical materials produced by the Branch were completed. This is the first phase of a continuing effort to establish a unified visual communications system for the NIH. New equipment and a broadening in personnel skills through training contributed to improvements in Branch services.

5. Veterinary Resources Branch

Total issues of VRB-produced small animals remained at about 500,000. Inbred mouse production increased slightly over last year despite two problems which required phasing out some production colonies and reestablishing them. The colonies in question were affected by a Sendai virus contamination and a genetic contamination.

Following the discovery of genetic compromise, the foundation colonies of BALB/c, A/HeN, and AKR/N mice were tested extensively for genetic integrity. Skin grafting, test mating, mixed lymphocyte cultures, and biochemical tests were performed. All indicated the foundation colonies were unaffected, allowing reestablishment of the production colonies.

Contract-purchased small animals increased from about 84,000 animals last year to about 150,000. New contracts were established for Hartley guinea pigs and inbred mice and rats.

The VRB genetic repository of small animals supplied more breeding nuclei to establish new colonies outside of the NIH than in any previous year. All major National Cancer Institute small animal contract programs are now relying upon VRB as the genetic base for their colonies. Germfree and pathogen-free animals were provided as pedigreed nuclei for the Frederick Cancer Research Center and other Division of Cancer Treatment and Division of Cancer Cause and Prevention contractors. This is the first year DCT has utilized this resource.

Barrier maintained mouse and rat colonies are now being fed a new open formula autoclavable ration containing 18 percent protein instead of a 24 percent commercial ration. The new ration, developed by the VRB nutritionist, is expected to bring a 25 percent saving.

NIH use of dogs was the lowest of any year on record, declining 25 percent from fiscal 1975. The breeding of larger animals such as goats and burros increased in scope, as did the breeding of purebred foxhounds at the Animal Center section. No random source dogs were used.

The Animal Disease Investigation Service experienced a 59 percent increase in the number of calls over the previous year. This service continues to be mutually beneficial to BID investigators and the VRB professional staff.

A computerized recordkeeping system is being developed for use in small animal breeding, colony management, and in the collection of pathology and clinical data on primates used in research.

The Experimental Surgery Unit of the Veterinary Medicine and Surgery Section was relocated from Building 28 to larger quarters in Building 14E. Renovations to Building 14D, due for completion in the fall of 1976, will create a holding capacity for over 1,800 nonhuman primates for infectious disease and other intramural programs.

More than 3,000 rhesus monkeys were quarantined and issued with more than 550 going to NIH intramural breeding programs. Contract breeding programs reached their projected capacity with a total of more than 1,500 breeding rhesus monkeys.

D. Division Management

1. Personnel Appointments

Mr. Barry Rubinstein and Mr. Ronson Britt were appointed Personnel Officer and Equal Employment Opportunity Officer, respectively.

2. Employee Development

During the year selected employees were trained in executive development, organizational development, management and career planning. Seminars were presented on merit promotion, employment of the handicapped, modern management for secretarial personnel, and personnel policies and procedures. An internal supervisory training program meeting Civil Service Commission requirements was established. The Training Office staff interviewed all DRS employees at the GS-9 and below levels and arranged for training designed to meet special needs. Several employees participated in Adult Education and Upward Mobility training programs.

3. Management Analysis Projects

Analysis Office projects included a study of service and supply fund billing systems; studies of small animal and primate information systems; a study of work improvements which led to implementation of recommendations to redistribute available manpower, install automated systems, and modify current processing procedures in the Glassware Unit, Environmental Safety Branch.

4. General Administration

The Division's Executive Officer and Budget Officer were appointed to the NIH Central Service Activities Task Force. We believe it is important that the work of this group result in the development of ways for providing central service activities with

- advance BID program plans that are definitive and accurate
- a meaningful and timely budget formulation and financing process.

If both of these objectives are realized, there can be improved program planning and development to more responsively and efficiently meet NIH needs for central support services.

The Division provided administrative support for the Interagency Primate Steering Committee in its efforts to develop a national plan for the breeding and distribution of non-human primates needed in biomedical programs. DRS provided space, financing, and personnel resources for committee staff members on an interim basis. A permanent resource allocation decision is pending.

5. Equal Employment Opportunity

Certain changes in personnel procedures resulted from suggestions of the Division's Human Relations Committee. A promotion route sheet check list was developed to keep employees and management better informed of the status of promotion recommendations. Special leave procedures were revised to clarify the appropriate means and circumstances for their use.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1975 through June 30, 1976

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Robert L. Dedrick
Acting Chief

I. SUMMARY

Major projects undertaken during the year were characterized by many complex and frequently contradictory technical and biological constraints. They generally pushed the limits of knowledge and required close and continuing collaboration among professional and technical staff from several disciplines. Project goals are subject to revision and refinement as collaborative interaction occurs and new technology is developed. The extent of collaboration is indicated by the attached bibliography in which 52 of the 63 cited publications and patents (83%) bear joint authorship between Branch staff and biomedical scientists.

Most of the individual projects had objectives to observe, describe and analyze biological systems at various levels or organization in vitro or in vivo. They ranged from the biochemical through the cellular or tissue to the whole body. At the biochemical level, a number of instruments and methodologies were developed to observe structure, composition and reaction rates. They included: a pulsed Fourier transform nuclear magnetic resonance spectrometer usable for several nuclei; a thermal titration apparatus capable of measuring heats of reaction associated with chemical reactions of protein such as acid/base titration; and an improvement of atomic absorption spectrophotometry to permit assay of trace amounts of endogenous or exogenous metals in biological specimens. Active development continued on a potentiometric titration system under the control of a dedicated microprocessor and a laser-excited temperature-jump apparatus for fast kinetic studies.

At the level of the cell or tissue in vitro, several techniques were investigated and instruments developed. The optical-thermal properties of liquid crystals were examined for relevance to temperature measurements on the size scale of a single cell. A capillary membrane-based tissue culture unit, developed in an earlier collaborative project, was instrumented and analyzed to permit rigorous metabolic studies on mammalian cells grown to tissue-like density. Measurements of hypertrophy and phosphorylation of muscle preparations are made possible by an integrated isometric myograph and optical system. The organ culture unit is easily adapted to a variety of tissue preparations including embryological systems.

Our physiologic understanding and diagnostic capabilities have been greatly enhanced by a number of related theoretical and experimental developments. Principles of chemical reaction engineering have been applied to the distribution of drugs, environmental contaminants, and endogenous metabolites in animals and man; this leads to more quantitative specification of anti-cancer drug therapy and provides operational bases for extrapolation between species.

Low level fluorescence, oxygen consumption, and microelectrodes have been combined to investigate cortical metabolic activity and potassium transport. Fluorescence technology also promises important contributions to the assessment of cardiac muscle condition during surgery. Theoretical factors governing the interpretation of Doppler ultrasound were thoroughly investigated, and diagnostic ultrasound was advanced by the addition of velocity measurement at a selected point of a two-dimensional scan. The feasibility of fluorescence spectroscopy at the microscopic level *in vivo* has been established by a device employing miniature fiber optic probes. Local uptake and removal of fluorescent marker molecules can be observed, and the technique may be applicable to measure metabolic activity of tumors and normal tissue.

Considerable progress was made in observing, describing, and analyzing nonbiological systems such as prosthetic materials or devices and model systems. A clearer understanding of the interaction among design features, materials properties, and the biological environment has emerged from successful heart assist devices, ventricular-aortic by-passes and composite heart valves. Novel design concepts are being explored to develop a miniature catheter capable of insertion into small convoluted blood vessels. The wall shear stress distribution has been measured in a model of a canine aorta by an electrochemical technique, and fluid dynamic phenomena correlated with the location of atherosclerotic lesions. Mathematical models of particulate hydrodynamics are making important contributions to our fundamental understanding of transport in synthetic and biological membranes.

The technical service sections are being strongly oriented toward research support with a greater emphasis on training, participation in technical societies, direct involvement with professional staff, and encouragement of initiatives in technology development. Efforts are underway to obtain routine and production type work by contract. Contracting and overtime have reduced the response time in our Systems Maintenance Section to an acceptable level; however, heavy backlogs remain in the Instrument Fabrication Section. More extensive use of fabrication contracts is being developed, but it has not had a program impact this year. The Scientific Equipment Rental Program has continued to expand, and its integration into the repair program makes more replacement equipment available.

II. BRANCH PROGRAMS

A. Objectives

To provide direct and consultative engineering support to clinical and biomedical research programs including systems analysis, research design, and innovation of relevant new technology.

To design, develop, fabricate and evaluate special purpose devices and systems not commercially available.

To maintain, modify, and repair scientific laboratory and clinical equipment.

To serve as a national focal point for biomedical engineering and provide communication between the NIH and the larger scientific, educational, and technological community of which it is a part.

B. Current Programs

The primary mission of the Branch is to provide engineering and technical services to the intramural program of the NIH. Its organization is both functional and disciplinary in order to provide flexibility to management and preserve the concept of professional and technical peer groups at the operating level. Specific activities are closely identified with the individual programs that constitute the intramural research effort.

1. Engineering and Applied Science -

Chemical, Electrical and Electronic, and Mechanical:

a. Direct and consultative professional services to fundamental and applied projects within the intramural programs.

b. Research, design, development, and evaluation related to biomedical engineering science and practice.

c. Communication within NIH and between NIH and the scientific community on the application of engineering to problems in biomedical research and clinical medicine.

2. Technical Services -

a. Design, fabrication, and modification of biomedical equipment and instrumentation systems requiring technical skills and special tools in electronic, electrical, glass, mechanical, optical, plastics, elastomeric, sheet metal, and welding categories.

b. Maintenance and repair of biomedical equipment and instrumentation systems and instruction of scientists and technicians on their proper use and operation.

c. Rental of general purpose scientific apparatus.

d. Acquisition and disposition of materials, parts, and equipment required for Branch operations and maintenance of controlled inventory stocks and records.

C. Program Progress and Accomplishments

1. Engineering and Applied Science

a. Chemical Engineering

Principles of chemical reaction engineering were successfully applied to a variety of parmacokinetic problems. (1) Clinical studies emphasized intraperitoneal and intrathecal drug administration. The analysis suggested that the predominant mode of methotrexate transfer from the central nervous system to the systemic circulation is bulk flow adsoprtion of CSF. (2) A pharmacokinetic model was developed for the distribution and disposition of actinomycin-D in the beagle dog. The model indicated that uptake of actinomycin-D by most tissues is limited by blood flow rates but that transport to the testes is restricted. (3) Because of an increased interest in marine species as experimental animals, phenol-red was modeled in the dogfish in order to document its relevant pharmacokinetic parameters. (4) A pharmacokinetic model assisted in the investigation of the distribution, metabolism and excretion of several isomers of the ubiquitous environmental contaminants, polychlorinated biphenyls, in the rat. The model provided for simultaneous consideration of the lipid soluble parent compound, water soluble metabolites, and the metabolism of PCB's by the liver. It can be extended to make predictions of PCB concentrations in higher animals and man.

Considerable work was conducted on instrumentation and measurement techniques. (1) A method for microthermography was investigated which utilizes the optical-thermal properties of liquid crystals. A major effort was undertaken to establish whether highly purified cholesteric esters could provide sufficient sensitivity and resolution for individual cell chemistry. (2) As part of studies aimed at improving the methodology for hollow fiber cell culture and at investigating the response of cultured cells to pharmacologic agents, developmental work is proceeding on systems for monitoring the rate of oxygen consumption and the extracellular oxygen partial pressure by employing mass spectrometry and miniature oxygen electrodes. These studies will help to elucidate the factors which maintain and promote cell growth. (3) Work has continued on improved methods of quantification, identification, and characterization of trace metal species in biological tissue samples by flameless atomic absoprtion spectrophotometry. Sensitivity has been achieved in the picogram to nanogram range in milligram sample sizes. Binding of platinum to plasma proteins has been studied, the iron content of purified enzyme has been confirmed and other activating metals sought. Trace metals in the blood serum of alcoholic rats on litium therapy have been measured, and the effect of adriamycin on calcium binding in heart muscle has been investigated.

Biomaterials studies emphasized the investigation of physiochemical factors which are desirable to make compatible implant devices. The techniques deemed necessary to characterize suitable materials include scanning electron microscopy, infrared spectroscopy, contact angle measurements, tensile property measurements, and energy dispersive x-ray analysis. A variety of prostheses have already been employed in animal experiments. No lipid absorption was observed on heart assist devices of polyurethane implanted in calves for up to 35 weeks. Physical strength remained stable, and the elastomeric surface developed a biocompatible layer of protein. Ventricular-aortic bypasses have functioned satisfactorily up to 17 weeks in dogs with negligible blood damage. Several prosthetic ball-and-cage heart valves have also been implanted in calves and their performance and properties observed.

Studies in biological fluid mechanics have included wall shear measurements in a model of a canine artery and particulate hydrodynamics in porous membranes. (1) The model studies show that the shear rate on the surface of the artery varies considerably from point to point, and that the unusual distribution of shear can be attributed to the intricate geometry of the flow network. The topographic distribution of arterial lesions in test animals which were maintained on an atherogenic diet correlates with regions in the model that have high shear rates or disturbed flow patterns. (2) Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions in order to provide a predictive theory to account for such observations as "hindered diffusion." The Taylor-Aris analysis has been extended to treat combined Brownian motion and convection in a single pore. Perturbation techniques have been used to obtain asymptomatic solutions to the hydrodynamic equations, and the method of moments was employed to analyze the solute continuity equation.

Extensive consultation was provided to a variety of intramural and collaborative programs.

b. Electrical and Electronic Engineering

BEIB completed a substantial number of new designs for electrical and electronic apparatus for the NIH research programs. Projects deserving special mention are summarized as follows:

Progress in clinical instrumentation was marked by further development of the use of low light level TB fluorescence measurements to monitor cortical metabolic activity, and extension of the technique to assessment of cardiac muscle condition during open heart surgery. A major effort in diagnostic ultrasound was the addition of Doppler velocity measurement at a selected point of a two-dimensional scan. In addition, theoretical factors governing interpretation of the Doppler signal were thoroughly investigated. Further progress was made in utilizing video techniques for generating visual test patterns and for recording and displaying many types of physiological data.

In the area of laboratory instrumentation, a major advance was completion of a Fourier transform nuclear magnetic resonance system which can easily be switched to any nucleus which is resonant in the 5 to 105 MHz range. An ultra high speed temperature-jump apparatus is under development, with Q-switched laser excitation, for fast kinetic studies. A third generation thermistor bridge was developed for differential microcalorimetry.

A new program initiative was undertaken to promote the application of microprocessors to clinical and laboratory instruments. Completed projects include a potentiometric titration system and an oxygen dissociation apparatus.

The patient electrical safety program continued with increased emphasis on training of the nursing staff and on greater use of the computer for scheduling inspections and analyzing data.

Extensive consultation was provided to a variety of intramural and collaborative programs.

c. Mechanical Engineering

Continued collaboration with research programs and with instrument implementation problems throughout the NIH has resulted in significant advances in many areas.

An instrument has been developed and successfully tested in humans which enables neurophysiologists and neurosurgeons to obtain electrical recordings from single nerve cells in the cerebral cortex during surgery. The device permits a microelectrode to use the pulsating cortex surface as a reference point in such a manner that there is no damage to the tissue, and compensation is made for the relative motion which usually occurs between the electrode tip and the adjacent tissue so that the the tip remains in close proximity to an individual selected cell. The new technique makes possible the study of the roles of individual cells in the generation of epileptic seizures, the control of movement, speech, vision and other normal and abnormal functions of the brain. Intracellular recordings of many minutes duration have been achieved in monkeys, and this technique will be extended to humans.

A family of thermal titration instruments for study of the chemical kinetics of protein continues under development. These instruments permit sensitive and very rapid measurements to be made when acids and bases are titrated and mixed. Temperature changes of 0.00025° C/scale centimeter and heats of reaction with a resolution of 2×10^4 calories per scale centimeter are observed. A differential version of the existing apparatus is currently under development. In a related project, an instrument for generating the oxyhemoglobin dissociation curve within minutes using a 1/4-ml sample is being tested.

Substantial progress has been made in a program utilizing miniature fiber optic probes for a variety of *in vivo* measurements. In one project, the transport of fluorescein in tumor and normal tissue is being monitored using a fluorescence technique. Pairs of single optic fibers carry light from a high power lamp to the tissue, and from the tissue to a sensitive photomultiplier tube. Conjugation of fluorescein to various materials will enable fundamental studies on transport within the tissue to be performed. The technique will be extended to the investigation of tissue metabolism. The technique is also being developed for *in vivo* measurement of tissue pO_2 and ph for use in patients with sickle cell anemia or pulmonary disease.

A life support system for muscle preparations *in vitro* has been under further development. Papillary muscle has been maintained for study over 48-hour periods. Among the studies being pursued are muscle hypertrophy and phosphorylation of isolated living muscle.

Another life support, or tissue culture, system has been developed for the study of normal and abnormal palate closure (cleft palate). Tissue from fetal mice is maintained in vitro for approximately two days during observation of palate formation. The study will continue with the use of selected reagents which may help or hinder palate closure.

Miniature catheters are under development for insertion into small tortuous vessels to study delivery of therapeutic material directly to the site of tumors and other lesions. Mechanization and automation of routine laboratory and glassware procedures are being extended and improved.

Substantial advances were achieved in fundamental and applied research on concomitants of CNS trauma, particularly in examination of the relationship between electrical conduction in nerve fibers and mechanical shock. There have been continued advances in protection of clinical personnel handling radioactive materials and in the refinement of the processing of electrophoretic preparations. Application of fluidic logic and control to the programming of reagent inputs to a rapid reaction stop-flow calorimeter continues.

A new family of instruments for use in eye surgery is being refined and further developed. These include a vitreous humor extractor and a sub-retinal fluid drainer. The development of a system to remove a quick-freeze brain tissue preparation continues. This includes reduction of the tissue to submicron particles and removal of mitochondria from cell nuclei for further assay.

Extensive consultation was provided to NIH programs.

d. Florence Agreement

BEIB is responsible for implementing NIH commitments related to the "Florence Agreement." Duties involve review of applications for duty-free entry of foreign manufactured scientific apparatus acquired by domestic nonprofit institutions, assessment of the suitability of equipment cited for intended applications, investigation of availability of domestically produced scientific equivalents, recommendations to the U.S. Department of Commerce for approval, disapproval, or resubmission; and providing pertinent technical advice to requesting agencies and the Department of Commerce. Activities for FY 1976 are summarized as follows:

Number of applications recorded by NIH	600
Referred to other agencies	180
Processed by NIH	420
Processed independently by the Executive Secretary	400
Processed with help of other Committee members	20
Recommendations for approval	330
Recommendations for disapproval	20
Recommendations for resubmission with more information	70

As an aid and guide to scientific judgment of the relative capabilities of domestic and foreign instruments, standardized test specimens have been developed for transmission and scanning electron microscopes. In addition, a test phantom was designed and constructed for assessing contrast sensitivity, spatial resolution, radiation dose, and other parameters of x-ray computer-assisted tomographic systems.

2. Technical Services

a. Instrument Fabrication Section

Heavy backlogs (approximately two months) continue due to manpower ceilings. Steps are being taken to help reduce this delay in the future by means of contracting certain routine fabrication jobs. Patient care related projects received first priority. Substantial overtime enabled the Section to complete 3,400 jobs valued at $867,000 without sacrificing quality compared with 3,600 jobs valued at $900,000 in FY 1975.

b. Systems Maintenance Section

Through the use of contracting and overtime, the average response time has been reduced from two weeks to two days for routine maintenance work, and to less than one day for emergency requests. A program has also been initiated to make replacement equipment available to investigators through the rental program while their equipment is awaiting repair. The rental program manager monitors all service requests, and the appropriate unit supervisor is notified if a suitable replacement is available in the rental pool. To further this program, selected instruments that are usually repaired on contract have been purchased and added to the rental pool.

In-house training programs have been initiated which will enable employees to repair and modify more complex equipment and to better understand the needs and requirements of the scientific community. A year-long course has been developed for the mechanical unit which includes a review of the basic principles of physics and their application to the operation and repair of selected pieces of scientific equipment. Individual short courses are being offered in the electronics units on the repair of selected scientific instruments. Lectures on various types of scientific instruments are also being presented which cover the basic principle of operation and the chemical and/or biological significance of the parameters measured.

The Scientific Equipment Rental Program has continued to expand over the year as summarized below:

	July 1, 1975	July 1, 1976	Percent Increase
Number of pool items	550	590	7%
Dollar value	$700,000	$850,000	21%
Number of items on rental (Yearly Average)	244	268	10%
Utilization Rate (Yearly Average)	44.3%	45.5%	2.7%

c. Supply Unit

An effort was made throughout the year to achieve greater economy by consolidating inventories in terms of capital investment and number of items carried. A comparison with FY 1975 operations shows a change in number of transactions processed from 22,000 to 23,000 with the value of goods sold increasing from $440,000 to $493,000 in FY 1976.

3. Selected Technical Advances

An instrument for obtaining intracellular recordings from pulsating monkey cortex. A gas bearing suspension system enables the tip of a recording microelectrode to locate, penetrate, and remain inside a neuron without damage to the cortex.

Measurement of wall shear stress distribution in model of canine aorta by an electrochemical technique in order to correlate fluid dynamic phenomena with location of atherosclerotic lesions.

An ultrasonic sector scanner for real-time opthalmic imaging. The system employs a 5 MHz bandwidth to provide high resolution in the axial direction. With this system eye motions can be recorded ultrasonically and examination time is reduced considerably.

A sonar micrometer for evaluation of regional contractility for canine myocardium.

A range-gated ultrasound Doppler flowmeter which permits experimental verification of theoretical resolution limits. Knowledge of resolution properties is required for optimal design and application of the general class of flowmeters.

A mathematical model for the distribution and disposition of phenol red in the dogfish shark to demonstrate the suitability of the dogfish for use in pharmacokinetic studies of antitumor drugs and environmental contaminants.

A special purpose frequency synthesizer for use in a pulsed Fourier transform NMR system with the capability of handling any nuclear resonance within the 5 to 70 MHz range.

An additive tricolor mixer capable of continuous variation in hue and saturation to be used in studying color vision in humans.

Miniature coaxial electrodes for electromyography of human occular muscles.

A high performance servomechanism for oscillating a primate during neurological studies of the vestibular-occular reflex. This device utilizes a high power brushless torque motor inside a feedback loop to achieve high stiffness and stability together with fast dynamic response in order to precisely follow electrically generated command signal waveforms.

Prostheses designed to replace selected vertebrae of prematurely exteriorized monkeys which have undergone forelimb deafferentation. No adverse reactions have been observed with the devices throughout replacement in the uterus, subsequent natural birth, and follow-up of several weeks. The prostheses offer natural movement, protective support of the spinal cord, and tissue compatibility.

A system that will maintain a population of mouse tumor cells at constant cell density while automatically monitoring the growth rate of the cells. The system will be used to evaluate the toxicity of various anti-tumor compounds.

A video pattern generator with a wide variety of static and dynamic displays, and provision for patient adjustment of perceived relative intensities. Patient reaction to the displays will be utilized to diagnose various abnormalities of the CNS.

A system for electronically sensing bacteria growth in a group of blood cultures and processing the data with a programmable calculator so as to make faster and more reliable determinations.

Analytical methodology and instrumentation for quantitation of nanogram amounts of platinum in biological tissue. An electronic slewing circuit on an atomic absorption spectrophotometer eliminates the requirement for chemical pretreatment of some types of samples and permits rejection of artifact on most others.

4. Training

Forty-eight employees participated in 96 academic, administrative, and technical courses. Twenty-three (153 man-days) undertook formal university education and training courses. Fifteen (67 man-days) received specialized training on scientific equipment at manufacturers' facilities and at the NIH. Fifty-three (93 man-days) attended various administrative, clerical, technical, and scientific courses and training seminars. Five employees were enrolled in the Upward Mobility College taking a total of 23 semesters of college-level courses.

D. Program Plans

The BEIB has the primary responsibility to provide engineering support and technical services to the intramural program of the NIH. Specific activities reflect both the needs of NIH and the human and material resources available to the Branch. As these resources are expected to remain severely limited for the immediate future, the Branch must attempt to optimize their use through closer and continuing interaction with NIH scientists in defining and pursuing those lines of development that are likely to be significant. It must also exploit resources that are available in universities, other government agencies, and the private sector to catalyze and direct their constructive relationship with NIH. Further, the Branch staff must be alert to opportunities for the development of new technology within its area of responsibility and be provided the environment in which creativity and initiative are both recognized and rewarded.

Specific plans pertain both to engineering and technical services.

1. Emphasize those projects which have known potential for significantly advancing our ability to (a) observe, describe, and analyze biological and nonbiological systems or (b) provide technology to clinical medicine.

2. Encourage service initiatives in developing new technology relevant to the mission of the Branch.

3. Develop our staff through in-house training, short courses, advanced study, research, and participation in professional and technical societies.

4. Exploit sources such as private companies and other government agencies for contract of routine or production type work or for required capabilities not available in-house.

5. Use outside staff on short-time or slot-free assignments such as through the Visiting Program, Intergovernmental Personnel Act, Stay-in-School Program, New Careers Program, and Guest Worker Program.

E. Publications and Patents

1. Publications

Allen, H.D., Goldberg, S.J., Sahn, D.J., Henry, W.L. and Griffith, J.M.: Medium for external acoustic transmission. In Proceedings of the 20th Annual Conference-American Institute of Ultrasound in Medicine, 1975, Winston-Salem, North Carolina. Winston-Salem, North Carolina, The American Institute of Ultrasound in Medicine, 1975, Vol. 20, p. 34.

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Goldstein, S.R., Schmidt, E.M., Bierley, F.L. and Bak, M.: A gas bearing mechanism for stable electrical recording from individual neurons in pulsating human cerebral cortex. Trans. ASME, J. Dynamic Systems, Measurement and Control 97: 234-242, 1975.

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2. Patents

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00001-08 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Acting Chief	BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	R.A. Bender	Oncologist	MB NCI
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	A.F. LeRoy	Chemical Engineer	BEIB DRS
	K.B. Bischoff	Prof., Chem. Engineering	Cornell University
	M.W. Anderson	Mathematician	EB NIEHS
	T.E. Eling	Pharmacologist	PB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	W.M. Galbraith	Pharmacologist	FDA
	H.B. Matthews	Pharmacologist	PB NIEHS
	W.A. Bleyer	Oncologist	Univ. of Wash.

COOPERATING UNITS (if any)
LCHPH-NCI, LT-NCI, PB-NIEHS, AK-CU Program NIAMDD, University of Washington, M-NCI, EB-NIEHS, FDA, Cornell University

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals and man. These provide operational bases for extrapolation from animals to man and for improvement of chemotherapy and hemodialysis.

PHS-6040
(12-75)

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide rational bases for extrapolation of toxicity from animals to to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of *in vitro* thermodynamic and kinetic data to *in vivo* cases.

(5) Predict effective dose schedules of anti-cancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physicochemical, physiological and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) Cerebrospinal fluid and plasma concentrations were measured in 76 patients who received intrathecal (lumbar) methotrexate. Following an initial rapid redistribution of the injected drug, the mean antifolate concentration in the lumbar CSF declined in a biphasic manner with half-lives of 4.5 and 14 hr. Pharmacokinetic analysis suggested that the predominant mode of methotrexate transfer from the CNS to the systemic circulation is bulk flow absorption of CSF. The two phases of disappearance appear to result from interaction of convective transport and diffusion between CSF and brain extracellular fluid (and perhaps some intracellular sites).

(2) A pharmacokinetic model was developed for the distribution and disposition of actinomycin-D in the beagle dog. Uptake and release of actinomycin-D by most tissues are limited by blood flow rates to the tissues. Transport to testes is restricted by a blood-testes barrier, and a linear membrane-limited model is required. Linear tissue binding is observed, presumably correlating with linear binding to DNA.

(3) A flow-limited multicompartment model simulates the distribution and disposition of phenol red in the dogfish after intravenous administration. Glucuronide conjugate, as well as parent compound, was found in urine and bile, but not in plasma, kidney, or liver tissue. An apparent four-hour lag in phenol red appearance in the gallbladder was simulated by two stirred

tanks connected in series to represent the bile ducts. The model should facilitate use of the dogfish in pharmacokinetic studies of drugs, environmental contaminants, and other xenobiotics.

(4) A pharmacokinetic model has been developed for the distribution and disposition in the rat of 4-chloro-, 4,4'-dichloro-, 2,4,5,2',5'-pentachloro-, and 2,4,5,2', 4',5'-hexachlorobiphenyl. The model required simultaneous consideration of the lipid soluble parent compounds and water soluble metobolites with conversion by metabolism in the liver. The metabolic clearance varied over a 200-fold range from 0.045 ml/min (hexachlorobyphenyl) to 10 ml/min (monochlorobiphenyl). Thermodynamic distribution coefficients and kidney and biliary clearances were also developed within the context of the model. Since the model is physiologic, it permits extrapolation to other species, including man.

Significance: Drugs and other chemicals are tested for effect in animals, and the extrapolation to man is a subject of serious concern. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events. Continued clinical emphasis through support of high dose and intraperitoneal protocols and other attempts to overcome drug resistance. Increased emphasis on environmental contaminants.

Publications:

Dedrick, R.L., Zaharko, D.S., Bender, R.A., Bleyer, W.A. and Lutz, R.J.: Pharmacokinetic Considerations on Resistance to Anti-Cancer Drugs. Cancer Chemotherapy Reports 59: 795-804, 1975.

Bender, R.A. and Dedrick, R.L.: Cytokinetic Aspects of Clinical Drug Resistance. Cancer Chemotherapy Reports 59: 805-809, 1975.

Lutz, R.J., Dedrick, R.L. Straw, J.A., Hart, M.M., Klubes, P. and Zaharko, D.S.: The Kinetics of Methotrexate Distribution in Spontaneous Canine Lymphosarcoma. J. Pharmacokinet. Biopharm. 3: 77-97, 1975.

Bischoff, K.B.: Some Fundamental Considerations in Applications of Pharmacokinetics to Cancer Chemotherapy. Cancer Chemotherapy Reports 59: 777-793, 1975.

Zaharko, D.S., Dedrick, R.L., Young, D.M., and Peale, A.L.: Tolerance of Long Term Methotrexate Infusions by Mice. Biochem. Pharmacol. (In press).

Zaharko, D.S. and Dedrick, R.L.: Antifolates: *In Vivo* Kinetic Considerations. Cancer Chemotherapy Reports (In press).

Bleyer, W.A. and Dedrick, R.L.: The Clinical Pharmacology of Intrathecal Methotrexate (NSC-740) I. Pharmacokinetics in Nontoxic Patients after Lumbar Injection. _Cancer Chemotherapy Reports_ (In press).

Litterst, C.L., Gram, T.E., Dedrick, R.L., LeRoy, A.R., and Guarino, A.M.: Distribution and Disposition of Platinum Following Intravenous Administration of cis-Diamminedichloroplatinum-II (NSC-119875) to Dogs. _Cancer Research_ (In press).

Bungay, P.M., Dedrick, R.L. and Guarino, A.M.: Pharmacokinetic modeling of the dogfish shark _(Squalus acanthias)_: Distribution, urinary, and biliary excretion of phenol red and its glucuronide. _J. Pharmacokinet. Biopharm._ (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00002-01 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. M. Bungay	Chemical Engineer	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intercellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptotic solutions to the hydrodynamic equations and the method of moments is employed to analyze the solute continuity equation.

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes which encompasses such observations as "hindered diffusion".

Methods Employed:

The essence of the approach is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogeneous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to the translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. When there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are perturbation techniques, both regular and singular, typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: Progress has been made in the expansion procedures for the hydrodynamic solutions in the two simplest models for neutral solute/neutral pore situations: spherical solute in a long cylindrical pore and in a long slit with plane parallel walls. Two limiting cases have been examined: solute diameter small compared to pore dimension, and solute and pore dimensions comparable in magnitude. A dispersion analysis has been formulated for the slit model following the treatment of Gaydos and Brenner for the circular pore model.

Proposed Course: In addition to the models presently under study it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle particle orientation and rotational Brownian motion effects. An ellipsoidal solute would theoretically be the preferred choice. A more desirable course is to incorporate into the present models non-hydrodynamical solute-membrane interactions such as electrostatic or London-Van der Waals attractive/repulsive forces.

Significance: Although channels (pores, slit-like gap junctions) represent one type of transmembrane transport in physiological systems, the conceptual framework of pore theory is helpful in biology as well as in engineering and the physical sciences.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00003-01 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	R. A. Knazek	Senior Investigator	LPP NCI

COOPERATING UNITS (if any)

LPP-NCI

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

SUMMARY OF WORK (200 words or less - underline keywords)

As part of studies aimed at improving the methodology for hollow fiber cell culture and investigating the response of cultured cells to pharmacologic agents, instrumentation systems are being developed for measuring relevant parameters. Under current development are systems for monitoring the rate of oxygen consumption and the extracelluar oxygen partial pressure. The instruments employed are a mass spectrometer and miniature noble metal oxygen electrodes. The latter may be operated in either voltaic or amperometric (polarographic) modes. Subsequent parameters to be investigated are pH and carbon dioxide partial pressure. Cell lines employed in the cultures are rat pituitary cells (GH1) and human choriocarcinoma cells (JEG-7).

PHS-6040
(12-75)

Objectives: The short-range objective is to develop sensor and instrumentation packages for monitoring cell metabolism and growth parameters of cells culturing in hollow fiber units. The long-range objectives are to: (1) elucidate factors which are beneficial to maintaining and promoting growth, and (2) determine the response of cells to pharmacologic agents.

Methods Employed:

The culture unit consists of a bundle of capillary fibers (typically 320, nominal diameters 200 μm ID, 250 μm OD) inside a cylindrical transparent polycarbonate shell. The extracapillary space at each end of the bundle is filled with potting compound. The cell suspension to be cultured occupies the remaining extracapillary volume. The hollow fibers act as a semipermeable barrier between the cells and the nutrient solution inside fibers. Tubing permeable to oxygen and carbon dioxide is used to form a closed sterile loop connecting the culture unit with a nutrient solution reservoir. A roller pump maintains a continuous recirculation of the solution.

The effort thus far has been to develop the capability to measure: (1) the rate of oxygen consumed by the cells in the unit, and (2) the extracellular oxygen tension in the culture. Under steady conditions, the amount of oxygen given up by the nutrient solution in passing through the fibers is a measure of the rate of consumption by the cells. The connecting tubing leading to the unit is of sufficient length that the nutrient solution is essentially saturated with respect to the ambient carbon dioxide enriched atmosphere. Measuring the ambient gas and effluent partial pressure and knowing the oxygen solubility in nutrient solution permits calculation of the rate of delivery of oxygen to the cells. The initial measurements are to be made using a mass spectrometer designed and calibrated for measuring oxygen and carbon dioxide partial pressures.

An alternative approach, and one more promising for the long-term, is to make potentiometric or amperometric (i.e., polarographic) measurements of the oxygen levels using noble metal electrodes. An electrode scheme has been under development for measuring the extracellular oxygen tension. The plan is to provide access for a fine wire electrode to the interior of a single nonporous, gas permeable fiber in the bundle. The fiber will extend beyond both ends of the bundle and through the walls of the distribution caps covering the ends of the shell. Thus, externally this fiber will be bathed by the nutrient solution inside the caps but be exposed to the cell culture inside the shell. The fiber interior will be otherwise isolated and can be filled with a buffer solution appropriate to an electrode pair such as platinum and silver/silver chloride. The oxygen sensitive cathode will be free to move axially inside the fiber such that it can be positioned to sense either the nutrient inlet, extracellular or nutrient outlet oxygen levels. Operated in an amperometric mode the system will function like a miniature Clark-type electrode.

Among the cell lines to be cultured are human choriocarcinoma (JEG-7) and rat pituitary cells (GH1).

Proposed Course: After satisfactory development of the oxygen monitoring systems, techniques will be examined for measuring other important cell culture parameters. Among the likely parameters to be looked at next are the pH and carbon dioxide partial pressure in the extracellular fluid.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00004-04 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Trace Element Analysis in Biological Materials

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. F. LeRoy	Chemical Engineer	BEIB	DRS
OTHER:	R. L. Dedrick	Acting Chief	BEIB	DRS
	A. M. Guarino	Chief	LT	NCI
	C. L. Litterst	Toxicologist	LT	NCI
	T. E. Gram	Toxicologist	LT	NCI
	T. J. Torres	Staff Fellow	LT	NCI
	D. M. Young	Veterinarian	LT	NCI
	C. K. Lee	Biochemist	LB	NCI
	L. Sokoloff	Chief	LCM	NIMH
	R. D. Hoeldtke	Biochemist	LCN	NIMH
	J. W. Boretos	Chemist	BEIB	DRS

COOPERATING UNITS (if any)

LT-NCI; LB-NCI; LCM-NIMH; LNC-NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.0	OTHER: 0.4

SUMMARY OF WORK (200 words or less - underline keywords)

Flameless atomic absorption spectrophotometry and neutron activation analysis have been used for quantitation of trace elements Pt, Ca, Fe, Li, and some others in biological tissues and fluids. The analyses are important in biochemical, pharmacokinetic and binding studies presently underway. Very sensitive analytical techniques are necessary because in most instances the elements are present in trace concentration and in many cases the sample size is very small as well.

PHS-6040
(12-75)

Objective: The objective of this work is to improve analysis and identification techniques for metal species in biological materials. Detection limits on the order of picograms to nanograms in milligram samples and simplified sample preparation have been sought. Quantitation of platinum, lithium, calcium, and copper, have been emphasized, while working with other elements of biological significance as interest develops.

Methods Employed:

Flameless atomic absorption spectrophotometry is being used principally for elemental analysis. Control of temperatures generated in a graphite furnace as a function of time permits analysis even when considerable molecular and broad-band absorption occur during combustion. Neutron activation analysis is being used to perform referee analyses.

Electrophoresis has been used to fractionate proteins with subsequent quantitation of metal species among the fractions. Improved resolution and analytical sensitivity are expected to result in findings of biological significance using these techniques.

Major Findings: These include sensitivity of platinum determination of 2 nanogram. Urine and plasma samples from animals treated with a platinum compound can be analyzed with no pretreatment although matrix effects must be taken into account. Other tissue analyses show that platinum concentrates in some tissues and is released very slowly if at all. Binding of platinum to plasma proteins has been studied to elucidate what chemical species are binding and what transformations occur with time. Iron content of purified enzyme has been confirmed and other activating metals sought. Trace metal levels in blood serum were measured in alcoholic rats receiving lithium therapy. Biochemical studies involving calcium binding are important in studies on the toxicology of adriamycin, and equilibrium dialysis experiments on cyclic-AMP. These studies require assay of very low concentrations of element or small sample size.

Significance: Quantitation, identification and characterization of metal species at trace levels in biological tissue samples, often very small, is important in biochemical research and environmental toxicology. Quantitation of a specific element in tissues and body fluids can help in understanding drug action and other biochemical processes. Methods being developed offer quantitation of very small quantities of stable elements and obviate the need for radiolabeled substances in some instances.

Proposed Course: Extend applicability of direct combustion technique to include more tissue types. Try to minimize or eliminate pretreatment required. Complete analyses for pharmacokinetic modeling of platinum compound, DDP. Perform necessary analyses for elements using neutron activation to confirm flameless atomic absorption spectrophotometry results.

Publications:

LeRoy, A.F.: Interactions of Platinum-Metals and Their Complexes in Biological Systems. Environmental Health Perspectives 10: 73-73, 1975.

Boretos, J.W., Pierce, W.S., Baier, R.E., LeRoy, A.F. and Donachy, H.J.: Surface and Bulk Characteristics of a Polyether Urethane for Artificial Hearts. J. Biomed. Mater. Res. 9: 327-340, 1975.

LeRoy, A.F.: Research on Environmental Contaminants-A Perspective. In LeRoy, A.F. (Ed.): Trace Contaminants in the Environment. New York, NY, American Institute of Chemical Engineers, AIChE Symposium Series No. 149, 1975, Vol. 71, pp. 1-3.

LeRoy, A.F. (Ed.): Trace Contaminants in the Environment. New York, NY, American Institute of Chemical Engineers, AIChE Symposium Series No. 149, 1975, Vol. 71, 56 pp.

Harder, H.C., Smith, R.G. and LeRoy, A.F.: Template-Primer Inactivation by cis-Dichlorodiammine Platinum for Human DNA Polymerase ∝ and β : The Mechanism of Cellular Cytotoxicity. Cancer Research (In press).

LeRoy, A.F., Wehling, M.L., Sponseller, H.L., Friauf, W.S., and Solomon, R.E.: Improved Control of Broad-Band Absorption During Analysis of Biological Materials by Flameless Atomic Absorption Spectrophotometry. In Epstein, S., Page, A.L., and Van Loon, J.C. (Eds.): Proceedings and Selected Papers from the International Conference on Heavy Metals in the Environment (In press).

Litterst, C.L., Gram, T.E., Dedrick, R.L., LeRoy, A.F., and Guarino, A.M.: Distribution and Disposition of Platinum Following Intravenous Administration of cis-Diamminedichloroplatinum-II (NSC-119875) to Dogs. Cancer Research (In press).

LeRoy, A.F., Friauf, W.S., Litterst, C.L., Gram, T.E., Guarino, A.M. and Dedrick, R.L.: Platinum Analyses in Animal Tissues and Fluids. In Proceedings of Platinum Research Review Conference, December 1975, Research Triangle Park, NC, U.S. Environmental Protection Agency (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00005-05 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	J. N. Cannon	Assoc. Prof., ChE	Howard University
	K. B. Bischoff	Prof., Chem. Eng.	Cornell University
	R. L. Dedrick	Acting Chief	BEIB DRS
	D. L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)
Howard University, Cornell University, OD-IR-NHLI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to elucidate the role of fluid dynamics and mass transfer in the onset and development of atherosclerotic plaques. Specifically, the wall shear stress was measured in a plastic model of a canine artery using an electrochemical technique to determine velocity gradients at the fluid-wall interface. Regions of high shear and of disturbed flow patterns in the model have been shown to correlate with regions of high incidence of lesions in animals on an atherogenic diet. These regions were near branches and flow dividers. The mechanism by which various flow patterns mediate increased lipid uptake by the arterial wall must still be determined.

PHS-6040
(12-75)

Objectives: Measure shear stress on the inner wall of plastic models of canine arteries during steady and pulsatile flow and correlate data with localization of atherosclerosis as found in experimental animals. Visualize flow patterns in the three-dimensional geometry of arterial branches. Measure the effects of shear on the transport rate of macromolecules through simulated and real arterial endothelium.

Methods Employed: An electrochemical technique is used, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface, which determines mass transfer rates of redox ions. Velocity gradients at the wall (shear rate) are calculated from mass transfer rates with suitable boundary layer equations.

Flow visualization can be achieved in a transparent cast of a canine artery by means of dye injection techniques and/or cinematography of latex microspheres.

Major Findings: In the arterial model, the shear peaks near the flow divider tips of branches; shear rate rises as flow enters smaller branches where velocity profiles are redeveloping. Shear drops suddenly just distal to the flow divider tips resulting in flow separation and flow reversal during pulsations. The shape of the shear pattern in the celiac artery is a function of the branch-to-approach flow ratio, but not of the total branch flow rate. The intricate three-dimensional geometry of the arterial tree and branching of the flow from the main channel are responsible for flow pattern characteristics. Regions of high shear and regions of disturbed flow patterns correlate with areas of increased plaque localization.

Significance: Elucidation of the role of hemodynamics and mass transfer in the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease.

Proposed Course: Verify electrochemical techniques experimentally and by computer simulation for measuring pulsatile shear stresses. Fabricate more realistic arterial models which include wall distensibility, and determine shear rate patterns. Devise mechanical models of the phospholipid membrane of arterial endothelial cells and determine the effect of shear on transport of macromolecules across these artificial membranes.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00006-11 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. W. Boretos	Physical Scientist	BEIB DRS
OTHER:	C. L. McIntosh	Senior Surgeon	SU NHLI
	A. J. Larrieu	Guest Worker	SU NHLI
	D. C. Syracuse	Clinical Associate	SU NHLI
	J. W. Prescott	Health Sci. Admin.	GD NICHD
	W. S. Pierce	Associate Professor	Penn State University
	R. E. Baier	Ph.D., P.E.	Calspan Corp.

COOPERATING UNITS (if any)

SU-NHLI, GD-NICHD, Pennsylvania State University, Calspan Corporation

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.8	1.5	0.3

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of polymers used for specific implants with the physiological environment and to explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts. Implants will be examined after removal for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves, vertebrae, and catheters will be employed. Observations should include SEM, infrared spectroscopy, contact angle measurements, tensile property measurements, and energy dispersive x-ray analysis.

Objectives: Elucidate the interaction of polymers used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic polymer composition is carefully controlled, and modification of cross-linking systems is employed. Rheological properties are studied as a function of cross-linking. Implants are examined after removal for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive x-ray analysis and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied *in vitro* in a test apparatus.

Major Findings: Twenty heart assist devices with segmented polyurethane blood contacting surfaces were implanted in calves for up to 35 weeks. No lipid absorption was observed; physical strength remained stable; surfaces developed a biocompatible layer of protein. Six additional assist devices have been implanted with similar results; four total heart implants have been achieved.

A series of ventricular-aortic by-pass devices functioned satisfactorily for periods up to 17 weeks in dogs with negligible blood damage.

Six segmented polyurethane covered polypropylene poppets housed in standard "Starr-Edwards 3M" cages have been implanted in calves. Three were electively removed after one year; no obvious physical or chemical changes occurred, and there was no evidence of injury to the animal. Two others showed marked tissue ingrowth into the suture ring area of the base of the valves and one thrombus on the metal struts of the valve cage.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart assist devices, vascular implants, and subcutaneous uses.

Proposed Course: (1) Extend experimental studies to further characterize the surface and bulk properties of polyether urethanes and more specifically determine its interactions with blood and subcutaneous tissue; and (2) study new designs of tricuspid heart valves for acute and chronic use.

Publications:

Boretos, J.W., Pierce, W.S., Baier, R.E., LeRoy, A.F., and Donachy, H.J.: Surface and Bulk Characteristics of a Polyether Urethane for Artificial Heart. *J. Biomed. Mater. Res.* 9: 327-340, 1975.

Boretos, J.W.: Silicones. In Kronenthal, R.L., Oser, Z. and Martin, E. (Eds.): *Polymers in Medicine and Surgery*. New York, NY, Plenum Press, 1975, pp. 87-98.

Boretos, J.W.: "Composite Heart Valve Poppet." U.S. Patent No. 3,911,502 (October 14, 1975).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00007-04 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Thermomicrography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. I. Peterson	Chemist	BEIB DRS
OTHER:	R. L. Bowman	Chief	LTD NHLI

COOPERATING UNITS (if any)

LTD-NHLI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a method for microscopic observation of biological cells by their thermal effects. A technique of microthermography would be useful for cell calorimetry and other energy studies on an individual cell basis and could provide a possible route to facilitation of screening studies involving various cellular reactions. The approach being taken is to attempt to use the optical-thermal properties of the cholesteric mesophase ("liquid-crystals"). A major effort had been undertaken to establish whether highly purified cholesteric esters would show properties improved over those usually available. The results, although interesting, did not solve the basic problems of resolution and sensitivity required for this application. An effort to achieve a better theoretical understanding of cholesteric behavior, which might provide a means to produce improved properties, has been difficult and not fruitful. Other possible approaches to solving the development problem remain.

PHS-6040
(12-75)

Objectives: Develop a method for microscopic observation of biological cells by their thermal effects.

Methods Employed: Investigation of the possible use of the optical-thermal properties of the cholesteric mesophase ("liquid crystals").

Significance: A technique of microthermography would be useful for cell calorimetry and other energy studies on an individual cell basis and could provide a possible route to facilitation of screening studies involving various kinds of cellular reactions.

Major Findings: A major effort to establish whether highly purified material would show improved properties, although giving interesting results, did not solve the basic problems of resolution and sensitivity required for this application. An effort to achieve a better theoretical understanding of cholesteric behavior, which could possibly be used to produce improved properties, was not fruitful. Other possible approaches to solving the developmental problem remain.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00008-04 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Diagnostic Ultrasound

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. M. Griffith	Electronic Engineer	BEIB DRS
OTHER:	W. L. Henry	Cardiologist	CB NHLI
	B. J. Maron	Cardiologist	CB NHLI
	H. J. Smith	Cardiologist	CB NHLI

COOPERATING UNITS (if any)
OD-NHLI, SU-NHLI, IR-NEI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

SUMMARY OF WORK (200 words or less - underline keywords)

Medical application of ultrasound is increasing at a rapid rate; BEIB is active in three instrumentation areas: (1) real-time imaging; (2) Doppler velocimetery; and (3) sonar micrometery. All three types of instruments are being developed for employment in a clinical setting. Although most foreseen uses are in cardiology, encouraging results have also been obtained in ophthalmology.

PHS-6040
(12-75)

Objectives: Noninvasively obtain dynamic images and measurements of cardiac structures and assess for diagnostic purposes.

Noninvasively obtain dynamic measurements of blood flow in circulatory vessels.

Obtain quantitative information concerning myocardial function in the post-operative period and as a function of drug dosage.

Methods Employed: A previously reported real-time, two-dimensional sector scanner was refined and used effectively in several new research applications.

Principles of high resolution radar and communication theory were applied to Doppler flowmeter design for improved spatial and velocity resolution.

A synthetic-aperture transducer is under investigation. It may provide improved spatial resolution for ultrasonic systems. A random-access memory design for a real-time scan converter is being considered for use in recording two-dimensional images. Such a converter would substantially reduce recording problems and improve the resulting images.

Major Findings: The resolution performance of pulsed ultrasound Doppler blood flowmeters is predicted by a simply analytical expression and is degraded linearly with an increase in the range at which velocities are measured.

It is feasible to employ a single transducer for cardiac imaging and for cardiac Doppler velocimetry. This greatly reduces the complexity of a duplex system.

Real-time, two-dimensional echocardiography is a useful tool for evaluation of arterio-ventricular valve morphology in congenital heart disease.

Presently available Doppler ultrasound systems cannot be employed to find shear stress at vessel walls as was previously hoped.

Publications:

Henry, W.L., Epstein, S.E., Griffith, J.M., Goldstein, R.E., and Redwood, D.R.: Effect of Prolonged Space Flight on Cardiac Function and Dimensions. In Proceedings of the Skylab Life Sciences Symposium, Houston, Texas, 1974, pp. 711-721.

Griffith, J.M. and Henry, W.L.: Switched Gain-A Technique for Simplifying Ultrasonic Measurement of Cardiac Wall Thickness. IEEE Transactions on Biomedical Engineering, July, 337-340, 1975.

Sahn, D.J., Henry, W.L., Allen, H.D., Griffith, J.M. and Goldberg, S.J.: The Comparative Utilities of Real Time Cross-Sectional Echocardiographic Imaging Systems in Complex Congenital Heart Disease. In Proceedings of the 20th Annual American Institute of Ultrasound in Medicine Conference, Winston-Salem, NC, 1975, p. 30.

Allen, H.D., Goldberg, S.J., Sahn, D.J., Henry, W.L. and Griffith, J.M.: Medium for External Acoustic Transmission. In *Proceedings of the 20th Annual American Institute of Ultrasound in Medicine Conference*, Winston-Salem, NC, 1975, p. 34.

Griffith, J.M. and Brody, W.R.: Resolution Performance of Pulsed Ultrasound Doppler Blood Flowmeters. In *Proceedings of the 20th Annual American Insitute of Ultrasound in Medicine Conference*, Winston-Salem, NC, 1975, p. 75.

Henry, W.L. and Griffith, J.M.: Sector-Scanning Echocardiography. In *Proceedings of a Conference on Cardiovascular Imaging and Image Processing: Ultrasound, Angiography, and Isotopes*, Stanford, CA, 1975, p. 4.

Griffith, J.M. and Brody, W.R.: Velocity Resolution in Ultrasonic Doppler Flowmeters. In *Proceedings of the 28th Annual Conference on Engineering in Medicine and Biology*. Arlington, VA, The Alliance for Engineering in Medicine and Biology, 1975, Vol. 17, p. 75.

Maron, B.J., Henry, W.L., Griffith, J.M., Freedom, R.M., Kelly, D.T. and Epstein, S.E.: Identification of Congenital Malformations of the Great Arteries in Infants by Real-Time Two-Dimensional Echocardiography. *Circulation* 52: 671-677, 1975.

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Griffith, J.M. and Henry, W.L.: Electromechanical Ultrasonic Scanning for Dynamic Cardiac Imaging. In Gramiak, R. and Waag, R. (Eds.): *Cardiac Ultrasound*. St. Louis, MO, The C.V. Mosby Co., 1975, pp. 228-244.

Smith, H.J., Goldstein, R.A., Griffith, J.M., Kent, K.M. and Epstein, S.E.: Selective Depression of Ischemic Myocardium by Verapmil. *The American Journal of Cardiology* 37: 174, 1976.

Griffith, J.M., Vita, A.J. and Henry, W.L.: A Moving-Trace Design for Video Systems. *IEEE Transactions on Biomedical Engineering* (In press).

Smith, H.J., Goldstein, R.A., Griffith, J.M., Kent, K.M. and Epstein, S.E.: Regional Contractility: Selective Depression of Ischemic Myocardium by Verapamil. *Circulation* (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00009-02 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. H. Schuette	Electronic Engineer	BEIB DRS
OTHER:	B. A. Vern	Clinical Associate	CNB NINCDS
	W. C. Whitehouse	Chief	AB CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS, AB-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism as indicated by the fluorescence of NADH and direct oxygen consumption measurements are being employed in the investigation of potassium ion kinetics in the cat brain. Research is being conducted in an effort to determine if the potassium clearance process following activation of the cortex is active or passive. An active energy-dependent process has been strongly suggested by several studies conducted as part of the program.

PHS-6040
(12-75)

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. In order to compensate for blood volume changes within the field of interest, a television fluorometer employing fluorescein dye as a reference was developed and employed.

A potassium sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous O_2 concentration difference multiplied by the flow rate.

For the Q_{10} experiments the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: A Q_{10} of 2.1 was measured for the potassium clearance rate constant. This is high enough to indicate an active process.

A strong correlation was found between oxidative metabolism from NADH fluorescence, direct oxygen consumption, and potassium kinetics indicating an energy dependent process.

The slowing of the potassium clearance during periods of hypotension demonstrated an oxygen requirement for potassium clearance.

Measurements of potassium levels in both the extracellular space and in the vascular system during and after seizure activity indicated a minimal transport to the vascular system as a part of the rapid clearance process.

Publications:

Schuette, W.H., Lewis, D.V., and Vern, B.A.: An Optical Flow Through Technique for Determining Cortical Oxygen Consumption in Cats. In Proceedings of the 28th Annual Conference on Engineering in Medicine and Biology. Arlington, VA, The Alliance for Engineering in Medicine and Biology, 1975, Vol. 17, p. 512.

Vern, B., Whitehouse, W.C. and Schuette, W.H.: Sodium Fluorescein-A New Stable Reference for the Fluorometric Measurement of NADH Changes in the Cat Cerebral Cortex. In Proceedings of the 28th Annual Conference on Engineering in Medicine and Biology. Arlington, VA, The Alliance for Engineering in Medicine and Biology, 1975, Vol. 17, p. 228.

Vern, B., Whitehouse, W.C., and Schuette, W.H.: Sodium Fluorescein: A New Reference for NADH Fluorometry. *Brain Research* 98: 1-5, 1975.

Lewis, D.V. and Schuette, W.H.: Temperature Dependence of Potassium Clearance in the Central Nervous System. *Brain Research* 99: 175-178, 1975.

Schuette, W., Lewis, D., O'Connor, M., and Van Buren, J.: The Design and Operation of a Dual Beam Long Focal Length Fluorometer for Monitoring the Oxidative Metabolism *In Vivo*. *Medical and Biological Engineering* (In press).

Mutsuga, N., Schuette, W., and Lewis, D.: The Contribution of Local Blood Flow to the Rapid Clearance of Potassium from the Cortical Extracellular Space. *Brain Research* (In press).

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Lewis, D. and Schuette, W.: NADH Fluorescence, $[K^+]_o$ and Oxygen Consumption in the Cat Cerebral Cortex During Direct Cortical Stimulation. *Brain Research* (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00010-01 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Automated Coulometrically-Controlled Potentiometric Titration System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. E. Clem	Electronics Engineer	BEIB DRS
	R. W. Hendler	Chief	LB NHLI
OTHER:	D. J. Songco	Electronics Engineer	CSL DCRT

COOPERATING UNITS (if any)
LB-NHLI, CSL-DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

SUMMARY OF WORK (200 words or less - underline keywords)

A Coulometrically-Controlled Potentiometric Titration System is being developed for the purpose of conducting potentiometric titrations, collecting data, and preparing the data for analysis in terms of the number of components present, their amounts, and their midpoint potentials. The developed system will perform the titration automatically, under the control of a dedicated microprocessor, which will also control data acquisition and storage for computer analysis.

Objectives: Develop an improved, automated method for performing potentiometric titration analysis for the purpose of defining the chemical constituents in certain organic materials.

Methods Employed: Develop and evaluate techniques for the control of the potentiometric titration by the injection of electrical current into the test solution, thereby forcing the titration through the direct addition or subtraction of electric charge in the test sample, and integration of the titrant control and data acquisition into a single unit with the microprocessor system.

Major Findings: Through the use of a system such as this, more accurate determination of sample constituents can be obtained in less time, with less direct human involvement than previously was possible.

Significance: This technique will allow research in certain areas involving potentiometric titrations to proceed at a more rapid rate than was possible before due to the ease of running a test sample, the faster data analysis possible with the computer interface, and the wide range of control of the experiment allowed by the microprocessor interface.

Proposed Course: To produce the system in a packaged form that can be used as a routine laboratory instrument.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 00011-06 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Nuclear Magnetic Resonance Techniques for Biochemical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. R. Clem	Electronic Engineer	BEIB DRS
	E. D. Becker	Chief	LCP NIAMDD
OTHER:	W. S. Friauf	Chief, EEES	BEIB DRS
	J. A. Ferretti	Research Chemist	PSL DCRT
	J. S. Cohen	Senior Investigator	RRB NICHD

COOPERATING UNITS (if any)

LCP-NIAMDD, RRB-NICHD, PSL-DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with the development of a pulsed FT nuclear magnetic resonance spectrometer. The outstanding characteristics of the instrument being developed are the capability of being usable for a wide range of nuclei that are observable over a range of frequencies from 5 MHz to 105 MHz and the ability to perform a variety of NMR experiments under control of the software in the minicomputer which controls the operation of the spectrometer. The system was designed using wideband circuitry wherever possible so that different nuclei can be observed with a minimum change in hardware being required. The system is presently being used as a routine laboratory spectrometer for the observation of ^{13}C and ^{1}H nuclei. Additional probes are now under construction to observe other nuclei which will utilize the wideband capabilities of the system. The spectrometer utilizes a commercial superconducting magnet and a commercial minicomputer with the remainder of the system being designed and constructed by BEIB. Other features incorporated in the system are: pseudo-random noise modulated proton decoupling, computer controlled gating of the decoupling, CW observation.

of protons for selective decoupling and shimming of the superconducting magnet field, deuterium observation for shimming and locking the superconducting magnet field, computer controlled homogeneity spoiling, and quadrature phase detection for signal-to-noise ratio enhancement and more efficient use of RF power.

Objectives: Innovate and implement improved methods for structural elucidation of organic molecules by means of nuclear magnetic resonance with emphasis on the capability of providing flexibility in the system for selecting one of several nuclei to be observed and the type of experiment to be performed.

Methods Employed: Develop and evaluate techniques for improving sensitivity and versatility, including use of a superconducting magnet, pulse train excitation using a minicomputer for producing the desired sequences, heteronuclear decoupling, real-time computerized data acquisition, digital averaging, phase correction, quadiature phase detection, Fourier Transformation and printout of spectra. Develop and evaluate Rapid Scan Fourier Transform NMR techniques as an intermediate alternative to CW and pulsed FT methods. Development of improved RF generation techniques for greater reliability and flexibility.

Major Findings: NMR techniques can be used to routinely obtain parameters of organic molecules beyond those previously available including nuclei other than ^{13}C and ^{1}H.

Significance: This technique offers unprecedented capability for elucidation of organic molecule structure in terms of location and couplings of a variety of atoms, primarily ^{13}C. The high field strength of the superconducting magnet enables finer resolution of nuclei distribution than is obtainable with most other NMR apparatus.

Proposed Course: BEIB will continue with the development and installation of some accessory equipment for the performance of specialized experiments, development of additional probes and hardware required for observation of some other desirable nuclei, and simplifying the operation of the system so that it is more readily usable by the scientific research staff with a minimum of knowledge of the technical operation of the system.

Publication:

Tucker, E.E., Clem, T.R., Seeman, J.I. and Becker, E.D.: Carbon-13 Nuclear Magnetic Resonance Relaxation in Hydrogen Bonded tert-Butyl Alcohol and Phenol. Journal of Physical Chemistry 79: 1005-1008, 1975.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00012-02 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Electrical Safety Program for Clinical Center Patients and Patient Care Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W. Friauf	Chief, EEES	BEIB DRS
	C. Strong	Environmental Services Officer	CC

COOPERATING UNITS (if any)
ADM-CC, SMS-BEIB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

SUMMARY OF WORK (200 words or less - underline keywords)

An electrical safety program has been instituted for the Clinical Center which includes the establishment of electrical safety standards, testing of patient-contact electrical equipment, training of nursing staff on the fundamentals of electricity, investigation of electrical accidents, surveying of electrical environment in patient care areas, counsel to medical staff on the purchase of new equipment and participation in the formation of national electrical safety standards. The program has resulted in a significant upgrading of the electrical environment in the Clinical Center patient care areas.

Objectives: Establish a patient electrical environment free of shock and burn hazard, assure Clinical Center compliance with electrical safety accreditation requirements and provide input to national organizations to assure realistic standards.

Methods Employed: In order to test the large numbers of equipment accurately and efficiently, two digital testers have been designed and built and the results computerized. Annual training seminars for nursing and other staff have been provided to the National Fire Protection Association regarding national standards for electrical safety.

Major Findings: The electrical safety program has found instances of overloaded circuits, excessive electrical leakage, non-isolated inputs, high leakage electrical power cable, and unrealistic national standards.

Significance: In all patient care areas the likelihood of electrocution or electrical burn has been reduced. In critical care areas, the staff and equipment are now providing care without subjecting the patient to undue electrical hazards.

Proposed Course: Perform statistical analysis on data gathered from the testing program to determine if changes should be made in test intervals and test standards.

Provide input into the design of new facilities and test new equipment and facilities before they are put into use.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00013-04 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Measurement of Low Level, Rapid Chemical Reaction Rates by Laser Jump, Temperature Jump, and Stopped Flow Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. I. Greifner	Electronics Engineer	BEIB DRS
OTHER:	F. J. Kollarits	Physicist	BEIB DRS
	P. B. Chock	Research Scientist	LC NHLI

COOPERATING UNITS (if any)

LC-IR-NHLI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	1.0	.25

SUMMARY OF WORK (200 words or less - underline keywords)

A laser temperature jump, capacitive discharge temperature jump, and a stopped flow apparatus have been designed for the fluoroscopic and spectroscopic detection of biochemical kinetic reaction rates. Improved system sensitivity and frequency response enable new exploratory investigations into the complex mechanisms of various enzyme functions. Kinetic reaction rate instrumentation can provide information on the incremental, fast interactions of antibiotics with enzymes or other proteins. Development of a new stopped flow cell reduced dead time from milliseconds to microseconds. Reaction rates previously masked by mixing can now be recorded. Pulsed bilateral energy from a Raman shifted Q switched Nd: Glass laser acts as a heat source to increase biochemical temperatures in nanoseconds. A pulsed high intensity xenon lamp used as an analyzing power source improves the signal-to-noise ratio of nanosecond and microsecond absorption measurements. Dynode switching of the photomultiplier detector provides wide dynamic range without impairment of frequency response, linearity or accuracy. Signal averaging techniques using computers recover low-level signals masked in noise.

PHS-6040
(12-75)

Objectives: Measure the incremental parameter changes corresponding to important biochemical reactions over a wide dynamic range. Design and develop a system capable of detecting, displaying and processing chemical reaction rates of less than 100 nanoseconds.

Methods Employed: Photomultiplier tubes are used to detect signal absorption and fluorescence. Dynode switching of the photomultipliers provides wide dynamic range without impairment of frequency response, linearity or accuracy. High intensity pulsed light sources improve the signal-to-noise ratio of nanosecond absorption measurements. Signal averaging techniques recover low-level signals otherwise masked by noise. The pulsed bilateral energy from a Raman shifted laser beam provides nanosecond biochemical temperature increases. Improved data processing reduces investigator evaluation time for a typical experiment from weeks to days.

Major Findings: A stopped flow system with increased sensitivity provides an order of magnitude improvement in absorption level detection over commercially available instruments. The stopped flow lead time is reduced from milliseconds to microseconds. This is accomplished by turbulent mixing in a newly designed cuvette.

Significance: State-of-the-art instrumentation for temperature jump apparatus and stopped flow meters can provide information on the incremental fast interactions of antibiotics with enzymes or other proteins.

Proposed Course: Select contractor for pulsatile and steady-state unit to power a high intensity xenon lamp. Design and develop laser temperature jump system for analysis of kinetic reaction rates in the nanosecond time domain. Evaluate and improve the new stopped flow cell.

Publication:

Rhee, S.G., Greifner, M.I., and Chock, P.B.: ATP Determination by Stopped-Flow Method. Journal of Analytical Biochemistry 66: 259-264, 1975.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00014-01 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Development of an In Vivo Micro Spectrophotofluorometer For Use In Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	P. M. Gullino	Chief, LPP	LPP NCI
	F. H. Grantham	Associate	LPP NCI
	P. M. Bungay	Chemical Engineer	BEIB DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.7	0.5

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop the technology and methodology to perform micro spectrophotofluorometry in caged laboratory animals using miniature fiber optic probes. Initial applications of the technique are to perform localized microwashout studies of tumors in rats using intravenously injected fluorescein in order to investigate variations in tumor local tissue perfusion. Future developments will hopefully include an extension of the technique to the study of metabolic behavior of tumors.

PHS-6040
(12-75)

Objectives: (1) To develop the technology and methodology required to make *in vivo* fluorescence measurements inside caged rats;

(2) Study the distribution and variation of local tissue perfusion inside tumors implanted in rats;

(3) Extend the technique to study tissue metabolism under controlled conditions.

Methods Employed: Pairs of single fiber optic strands are implanted along with tumor fragments in a rat. One fiber in each pair goes to a high intensity light source, the other fiber of each pair goes to a multiplexed high gain photomultiplier tube. Fluorescent dye injected into the cardiovascular system diffuses into the interstitial fluid of the tumor, is illuminated, fluoresces, and is eventually washed out. The time course of the fluorescence signal is then related to local tissue perfusion or other factors contributing to transport within the tumor.

Major Findings: The technique has been successfully employed using a prototype instrument. Fiber breakage and coupling problems have been solved. Protein deposition on the fibers and resulting opacity is not a problem, and signal-to-noise ratios are satisfactory using suitably low fluorescein concentrations.

Significance: Development of this technique will allow *in vivo* localized measurements in animals on a continuing basis that have not heretofore been possible. A great variety of experiments involving blood flow and metabolism will become possible which could enhance understanding of transport and metabolism in tumors and normal tissues.

Proposed Course: Improve sensitivity, and extend measurement capability to metabolically related substances; extend device family to related types of measurement requirements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00015-01 BEI

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheters for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J. L. Doppman	Chief	DR CC
	J. W. Boretos	Physical Scientist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this work is to develop miniature catheters for insertion into tortuous blood vessels as small as 1 mm diameter which are up to 15 cm long. Techniques of delivering embolizing material will be developed so that procedures previously requiring surgery can be performed instead with catheters. Topographic catheter and other novel concepts are being explored for this task.

PHS-6040
(12-75)

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels.

Develop techniques and devices for delivering therapeutic material into the catheterized vessel.

Methods Employed: Novel techniques, designs, and materials are being investigated, e.g., topographic catheters employing composite materials, etc.

Major Findings: Substantial further development is required to obtain a clinically useful tool.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels which are separated from larger, easily catheterized vessels by long narrow passages with numerous bifurcations. The ability to do this has tremendous implications for selectively treating tumors, aneurysms, and other lesions without endangering normal tissue.

Proposed Course: Continue exploratory and developmental work.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00016-01 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Thermal Titration Apparatus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	R. Berger	Senior Investigator	LTD NHLI

COOPERATING UNITS (if any)
LTD-NHLI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

SUMMARY OF WORK (200 words or less - underline keywords)

A thermal titration apparatus has been developed which permits the study of the small and rapid temperature changes associated with the chemical kinetics of protein. A reaction cell with a volume of 1 ml is maintained at a constant temperature (.005° C drift in 2000 seconds). Acid or base is delivered at a constant rate and rapid mixing is accomplished with a constant speed (± 0.5%) stirring system. pH and temperature changes are recorded. Testing has determined that the temperature, which is displayed on an x-y recorder, can be measured at 0.00025° C per cm scale and the heat of reaction is similarly monitored at 0.0002 cal per cm scale.
A differential version of the existing system is currently being developed which incorporates simultaneous optical measurements.

PHS-6040
(12-75)

Objectives: To design a device which enables one to study acid/base titrations of protein from pH and thermal changes with high resolution and rapid response.

Methods Employed: Equipment has been developed which consists of a constant temperature reaction cell (1 ml volume) (.005° C drift in 2000 sec), a constant speed titration system, a constant speed mixer (± .5% variation in motor speed) and a rapid response pH electrode and thermistor.

Major Findings: Temperature changes during acid/base titrations have been recorded on an x-y recorder with a resolution of 0.00025° C per cm scale. Also, the heat of reaction during acid/base titrations has been recorded with a resolution of 2×10^{-4} cal per cm scale.

Significance: The equipment permits calorimetric study of the chemical kinetics of proteins.

Proposed Course: To develop a differential version of the existing apparatus to improve accuracy, minimize sample volume and incorporate simultaneous optical measurements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00017-02 BEI

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

In Vitro Muscle Studies/Hypertrophy/Phosphorylation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	E. Lebowitz	Clinical Associate	CB NHLI

COOPERATING UNITS (if any)

CB-NHLI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

SUMMARY OF WORK (200 words or less - underline keywords)

The study of hypertrophy in isolated muscle preparations requires the maintenance of preparations for long periods of time (48 hours) and could consume large quantities of radioactive material. A unique organ culture apparatus for papillary muscle preparations was developed to protect the muscle from infection, prevent the release of contaminants to the environment, and minimize the amount of radioactive material required.

The apparatus contains an isometric myograph for detailed physiological studies. The preparations have been shown to remain viable based on physiological parameters (developed tension, and response to chemical changes). Data have shown that a protein which undergoes phosphorylation in the system has the same molecular weight as a subunit of myosin. The degree of phosphorylation is greatly enhanced (~2.5 times) in those muscles treated with norepinephrine for approximately 5 minutes compared to untreated controls running simultaneously. It is felt that the apparatus will enable detailed study of phosphorylation of muscle and its possible role in contractility. With minor modification the equipment could be applied to a variety of tissue preparations, particularly embryological systems.

PHS-6040
(12-75)

Objectives: To further develop the apparatus described in the annual report for the period July 1, 1974 to June 30, 1975.

To provide assistance with the design and implementation of an experimental protocol directed at the study of phosphorylation of living papillary muscle in isolation.

Methods Employed: Since large quantities of radioactive material are used and since the preparation is maintained for long periods of time (48 hours), a recirculating media organ culture system was developed. An isometric myograph was designed and integrated into the closed system.

Major Findings: A 19,000 Dalton protein has been shown to phosphorylate in the preparation. It is believed that this is a subunit of myosin. After the preparation is treated with norepinephrine for approximately five minutes the phosphorylation, as determined by the physiologic response, increases by ~2.5 times compared to controls.

Significance: Phosphorylation may be related to contractility and can be studied in detail with the apparatus developed.

Proposed Course: Improve and extend experimentation and analysis with particular concern for the biomechanical and transport aspects of the preparation.

DIVISION OF RESEARCH SERVICES

Summary of Program Activities July 1, 1975 through June 30, 1976

ENVIRONMENTAL HEALTH AND SAFETY PROGRAM

Dr. Rudolf G. Wanner
Associate Director

I. SUMMARY

1. Office of the Associate Director for Environmental Health and Safety

Reorganization of the Environmental Health and Safety Program to bring all elements of the program under central management was completed in January 1976. The program now functions through two operating units: the Environmental Safety Branch and the Radiation Safety Branch. Under the reorganization, the Environmental Safety Branch was expanded from two to four units. It now consists of the Environmental and Industrial Hygiene Section, Biological Control Section, Occupational Safety and Health Activities Section, and the Media and Glassware Section, which was transferred from the Veterinary Resources Branch. All functions of the original Environmental Services Branch and the former Safety Management Program, DRS, have been incorporated in the Branch's activities.

During the year, a periodic medical surveillance program was initiated for employees exposed to specific hazards. Activities required by the National Environmental Policy Act and other federal regulations were intensified to maintain NIH compliance. Training materials, such as films and other audio-visual aids, were developed, distributed, and presented. An information system on environmental health and safety for NIH employees was established, including an emergency hazard warning system. Special investigations of laboratory incidents were carried out, and the findings disseminated throughout the biomedical research community with recommendations for prevention.

II. BRANCH PROGRAMS

ENVIRONMENTAL SAFETY BRANCH

Vinson R. Oviatt, Chief

A. Objectives

The Environmental Safety Branch program is designed to locate and solve environmental problems; assure a safe, compatible environment for patients, staff, and the surrounding community; and promote an environment conducive to a quality research program.

B. Current Programs

1. Biohazards and Contamination Control

The biohazards and contamination control program maintains regular surveillance of potentially hazardous laboratory and animal room areas, control equipment, and facilities; laboratory safety consultation is provided on a case-by-case basis.

2. Industrial Hygiene

Gaseous and particulate air contamination potentially or actually generated at NIH and the laboratory use of chemical carcinogens are major surveillance activities. Problems of noise, temperature extremes, and non-ionizing radiation are investigated and resolved.

3. Hospital Environmental Control

The environmental control program in the Clinical Center protects patients, employees, and visitors from environmental influences which may be unsafe, unhealthful, or uncomfortable.

4. General Sanitation and Sanitary Engineering

The general sanitation and sanitary engineering program includes food sanitation, water supply, solid and liquid waste disposal, housekeeping practices, pesticides, and water pollution control.

5. Safety Management

The program objective is to reduce or eliminate accidents and to provide professional services required in the development, coordination, and implementation of occupational safety and health standards. It provides an accident reporting investigation and analysis services and the Branch training effort. It administers the Federal Employees Compensation Act for NIH employees.

6. Media Production

The media production program maintains, propagates and produces in large volumes a variety of continuous cell line tissue cultures to supplement BID requirements not met by commercial sources or individual laboratory preparation.

7. Glassware Production

The glassware production program decontaminates, sorts, cleans and inspects, prepares and reissues laboratory glassware to NIH investigators throughout the campus. It also furnishes cagewashing services to the Clinical Center.

8. Environmental Studies for Support of Research and Patient Care

Studies cover environmental systems and problems; evaluation of new equipment and methods; quality glassware and high purity water production; environmental stresses related to light, heat, noise, food, water, and waste; and the identification of environmental contaminants.

9. Training

Personnel training to promote job effectiveness concentrates on environmental control devices and practices which require special knowledge for proper operation and handling.

C. Program Progress and Accomplishments

1. Biological Control

More than 1,100 copies of the NIH Biohazards Safety Guide were distributed to interested individuals outside of NIH; 1,000 copies were distributed to laboratory chiefs and principal investigators at NIH. The quarterly memorandum, "Biological Laboratory Hazards," was distributed to more than 300 laboratories, including several overseas institutions.

An outbreak of tuberculosis in non-human primate colonies in Building 36 was investigated. When the diagnosis was confirmed, the animals were sacrificed and the room was decontaminated. All exposed personnel who were tuberculin test negative were being tested at regular intervals for antibody conversion.

Members of the Biological Control Section are serving on a committee of the National Sanitation Foundation, Ann Arbor, Michigan, to develop performance standards for Class II biohazard cabinetry. A final draft of the standard has been completed.

Consultations with individuals at NIH and outside NIH on equipment and other safety devices are shown in the following table (each consultation required on the average of four hours):

	NIH	Outside NIH
(a) Selection of Equipment	38	15
(b) Proper Use of Equipment	11	0
(c) Safety Devices and Biohazards Control	114	34

Three Memoranda of Understanding and Agreement were reviewed for work with recombinant DNA molecules and associated laboratory facilities were inspected and approved.

Modification of equipment included development of a warning device for Class II biohazard cabinetry to indicate when the unit is not operating properly. Sixty-five new Class II biological safety cabinets were installed at NIH. Three hundred and seventy-nine safety cabinets were tested to ensure that operator protection was provided. In addition, building system exhaust filters, vacuum system filters and sterilizers in biohazardous areas were tested and repaired as needed.

Twenty-seven plan reviews were conducted of major laboratory renovations at different stages of design. These included the renovation of laboratories in the Open Bay Area of Building 41; Building 3, 14D and E, 28 and 36. Approximately 15 draft reviews were made of such items as Manual Issuance #3031-1, "Control of Certain Hazardous Microbiological Agents in Intramural Research;" proposed Manual issuance concerning the importation of rodents and rodent products into NIH; and proposed federal specifications for filters and air conditioning systems.

A total of 8,733 bacteriological tests were performed in the analysis of patient food and milk, potable water and waste water, and other environmental samples. This is an increase of 12% over FY 1975.

Laboratory surveys are being conducted in those institutes where Class III and IV biological agents (CDC Classification) are used. As of April 1, 1976, 30 laboratory rooms had been surveyed.

The containment barriers in Building 36, 5C Virology Suite, were tested and recertified.

2. Industrial Hygiene

Staff participation in chemical carcinogen control was increased. Activities included membership in the laboratory Chemical Carcinogen Safety Standards Subcommittee, DHEW. The Committee is responsible for selecting chemicals of concern, development of monographs dealing with them, and assisting in development of control regulations. ESB provided technical support for the extramural carcinogen programs of NCI and responded to intramural problems.

The NIH chemical fume hood surveillance program was completed by contract in December 1975. Seven hundred sixty-seven hoods were checked with 111 of them found to be below the very minimum acceptable standard. Substandard hoods posing a handicap to investigators are being corrected.

Noise surveillance turned up problems ranging from nuisance conditions interfering with work effectiveness to adverse situations potentially harmful to hearing. Related activities involved a training and awareness program (250 people). Sixty NIH trucks were evaluated for conformance to minimum EPA/DOT standards.

More chemical spills occurred in research laboratory areas than in any previous year. There were several strong formaldehyde solution spills in Building 10A, mercury in Building 10, and divinyl mercury vapor releases associated with Building 4. A release of ethylnitrosourea in Building 37 involved major reaction of the Branch to the emergency. An emergency reaction plan was put into effect to funnel all emergencies through the NIH Fire Department.

Chemical carcinogen waste disposal procedures were published as an NIH Instruction and Information Memorandum (NIH-75-1) to help improve this aspect of NIH waste disposal procedures. Construction to upgrade the present NIH chemical waste disposal system was completed, and training and revised disposal procedures were developed in cooperation with the NIH Fire Department.

3. Hospital Environmental Control

The neurosurgery and heart catheterization laboratories in Building 10A were remodelled. Critical inspection of the renovated areas showed excellent control of the general sanitation and total environment.

The Baltimore Cancer Ward at the University of Maryland Hospital was inspected twice during the year. Continuing Aspergillus contamination of the air was found to be caused by the sound absorbent floc sprayed on the structural steel during construction. Spraying with a copper fungicide appears to control the release of viable mold spores from this material. Air currents from other areas inside and outside of the hospital contribute to the problem.

Air measurements were taken at six-month intervals in the Clinical Center operating rooms and heart catheterization laboratory. An environmental inspection was made of five nursing units (5-West, 6-West, 10-East, 11-West, and 12-East).

4. General Sanitation and Sanitary Engineering

As part of new EPA sewage treatment plant effluent requirements for federal facilities, a weekly sampling program was initiated at the NIH Animal Center. This program is a cooperative effort involving PEB/DES; Animal Transportation Section, VRB/DRS; and the Environmental Safety Branch, DRS. Sample containers and protocol were developed by ESB.

Complete semiannual food service inspections were made at NIH facilities operated by the Blind Industries and Services of Maryland and Government Services, Incorporated. In addition, Clinical Center patient care floor kitchens and main food preparation areas were inspected.

The solid waste system at NIH underwent a major change, with an equally major change expected in the coming year. ESB participated in a large number of facility and system reviews and carried the major workload of conversion to the paper bag/cardboard carton waste containerization program. This latter element is essential for compatibility with both the new pathological incinerator at NIH and the future Montgomery County Medical Pathological Waste Incinerator.

High purity water production is a priority program. Regular specific resistance measurements and a complete quarterly copper analysis of central distilled water systems were completed. Ten investigators received one or more special high purity water glass stills developed by ESB for special applications; nine are pending.

5. Safety Management

Calendar year 1975 represents the first full year of accident reporting under the HEW ADP system. NIH developed and implemented its own ADP input program which provides HEW with machine-readable data. The interface between the two systems has been highly successful. The NIH data system has been used locally in such special studies as accidents related to elevators, range of age of employees reporting injuries, and percentage of injuries reported which resulted in lost work time. It will also be used to provide the administrative staff up-to-date information as to where NIH safety problem areas are located.

The total claims for compensation filed during calendar 1975 increased significantly from the previous year. This was due in part to changes in the Federal Employees' Compensation Act which now permits continuing an employee in a pay status up to 45 days for loss from work as a result of a traumatic injury. Previously, lost-time injuries involving less than 21 days required a three-day waiting period in a non-pay status.

The Department of Labor furnished notices which were received and will be posted on some 58 official bulletin boards at the principal reservation and field stations. Safety news items are routinely published in the NIH RECORD. Posters are developed on a monthly basis and posted throughout the reservation. The "Environmental Health and Safety Special Investigation Report" was generated for appropriate incidents.

A new four-page "Environmental Health and Safety Report" was approved, with the first issue of this quarterly publication distributed to all employees. It is anticipated the publication will increase overall safety awareness and lead to the reduction of accidents.

6. Media Production

The number of requisitions processed for tissue culture and bacteriologic media increased 4.2% over last year; 74,000 liters of bacteriologic media and 71,000 liters of tissue culture media, for a total of 145,000 liters, were produced. This reflects a continued trend, noted last year, of increased production of bacteriologic media over tissue culture media.

Issues of blood agar plates of all types totaled 147,000, a slight decrease from last year. However, an additional 646,000 plates of other types resulted in a total plate production of 794,000. This is a 28% increase in total plate production over last year.

Issues of tissue culture cells as cell suspension showed a marked decrease of 50% with a total of 106 liters of suspension produced. Much of this decrease can be attributed to the difficulty in obtaining WI-38 cells in low passage.

Tissue culture cell freezing and storage services increased with a total of more than 2,500 ampoules of cells frozen, and over 2,900 ampoules of cells maintained in the frozen cell bank to support research programs requiring this service. This represents a significant increase of 31% over last fiscal year.

7. Glassware Production

Glassware issues to the Institutes and Divisions totaled approximately 8,262,000 pieces, a slight decrease from last year. In addition, there were 856 cases of disposable pipettes issued during the transition period between the use of reusable and disposable pipettes. A total of 262,000 cages, racks and associated pieces of equipment were processed.

In order to improve the efficiency of glassware production, the night shift operation was abolished and personnel transferred to the day shift. This move has proven to be beneficial in increasing production and improving employee morale. Shortages of personnel on both shifts made this move mandatory to provide maximum efficiency with the reduced manpower available.

A new glassware requisition form introduced in FY 1975 provided useful data on issues, as well as indications of how well the Unit is meeting demands for glassware. Additional information supplied in the form of percentages of each item ordered by size and type of glassware has been helpful in planning production.

8. Environmental Studies

A bioassay of Broad Run, the stream passing through the NIH Animal Center property, was completed. No adverse impact of the sewage treatment plant on the stream was detected.

Environmental levels and employee exposure to DDVP (2,2, dichlorodivinyl dimethyl phosphate) were evaluated in cooperation with VRB/DRS and the Employee Health Service, CC. This material is being considered for use in rodent cages for parasite control in selected areas of Building 14. The study did not indicate any health problem under the proposed use conditions.

The mold spore study in the Clinical Center was completed. Spores of Aspergillus species, Niger and Fumigatus are the most common isolates both in the Clinical Center air and the outside air, being most prevalent during October and November. This study was in collaboration with the Clinical Mycology Section, Laboratory of Clinical Investigations, NIAID.

Mold spores also were studied at the Westwood Building. Water seeped through the walls during heavy rain storms and was soaked up by both padding and carpeting. Subsequent mold growth provided excessive numbers of spores which were airborne. The carpet was removed and the wall sealed to prevent further occurrences.

9. Training

Training presentations using the slide/cassette packages on "Assessment of Risk," "Hazard Control in Animal Laboratories," and "Effective Use of Class II Safety Cabinets" were made to 85 laboratory personnel. Lectures on biohazard safety were given to 74 personnel outside of NIH.

Emphasis was placed on new employee orientation programs to safety and health matters associated with their work place.

A slide presentation, "Introduction to Biohazards Control," was developed and was made available for both intramural and extramural programs.

Demand for Branch personnel as lecturers and speakers in all facets of environmental health and safety remained high. Technical presentations were made at professional meetings at the local, national and international level. The staff lectured at short courses sponsored by other government agencies and served as faculty members at the University of Maryland and George Washington University.

ESB personnel received 2,323 hours of training at designated short courses or in classroom experience at colleges and universities. Three COSTEP trainees received on-the-job experience in the Branch.

D. Problems

More laboratory and storage space is needed to bring facilities up to applicable environmental health and safety standards. Currently, it is virtually impossible to provide needed ventilation or building renovations without significantly disrupting ongoing research. There is clearly a problem of diminishing returns if already congested laboratories are expected to absorb additional staff and equipment.

A widespread occurrence of defective tissue culture media caused by receipt of a mislabelled amino acid from the supplier pointed up the need for increased emphasis on quality control. While it is not economically feasible to test for each ingredient present in these complex media, certain concentrates employed in the production process lend themselves to analysis. Plans are underway to provide the necessary testing to detect deficiencies of this nature in future production.

Lack of adequate space for both personnel and automated equipment continues to be one of the major problems facing the Media Unit. Renovations to existing space on a piecemeal basis have only provided temporary relief, but the basic conditions of overcrowding in areas such as media storage at cold room temperatures and necessary expansion in bottling and plate pouring operations still exist. The increase in volume and complexity of requests for media makes additional space mandatory if these demands are to be met without greatly increased backlogs in production and deterioration in services.

E. Program Plans

The Branch programs will be restructured during the coming year to reflect the organization of the new Environmental Safety Branch. Organizational directives require that high priority shall be placed on surveillance and training activities with lesser attention to technical services. A study of applicable NIH, PHS, and DHEW policies and appropriate executive orders will assist in development of base line programs and services. The coordination of activities and services to the Office of Research Safety, NCI; the Office of the Director, CC; and the Division of Engineering Services will be required. Appropriate use of contractors and consultants will be studied to provide resources which cannot be provided by ESB staff.

To comply with the requirements set forth in The Convention on the Prohibition of the Development, Production and Stockpiling of Biological Weapons, which has been signed by the U.K., U.S.S.R., U.S.A., and 100 other countries, the Secretary, DHEW, has requested information on the type of certain very hazardous microbial agents and the types and amounts of toxins in use at the NIH. Because the registration of microbial agents, tissue culture and animals was proven to be satisfactory last year, the only change in the questionnaire to be sent to appropriate individuals will be the inclusion of a request for information on the types and quantities of toxins. The procedures for the entry, storage and retrieval of the information on the returned questionnaire will not be changed substantially.

It is planned to extend reservation-wide the NCI developed door sign system for identification of hazard level in each laboratory. A floor plan will be posted at laboratory building entrances to show where hazard areas are located.

A program will be implemented to supply each principal organizational entity within NIH a monthly report on their accident experience. The report will be a selective combination of qualitative and quantitative information available from the accident report data base and analysis by the staff.

NIH has had several safety committees functioning in the past. In some instances, these committees have gradually ceased to perform. The Occupational Safety and Health Activities Section will assist in restructuring them so that they once again will play a meaningful role in the health and safety program.

Quality control procedures will be expanded to focus on those areas of bacteriologic and tissue culture media which can be monitored with limited space and personnel. The possibility of contracting for those services not available in-house will be explored.

Several areas of media production which are available commercially on a routine basis will be reviewed for possible contracting in an effort to improve the response time for meeting demand. This plan will allow the Media Unit to concentrate more manpower in the area of specialized media production, which is either not available through commercial sources, or prohibitively expensive commercially.

F. Publications and Patents

DeRoos, R., Vesley, D., DuChene, A., and Hart, L.J.: High Purity Water

Supplies for Biomedical Research Laboratories. Health Laboratory Science. 13:1 11-19, 1976

Herman, L.G.: Sources of the Slow-Growing Pigmented Water Bacteria. Health Laboratory Science. 13:1 5-10, 1976.

Irwin, J., and Stoner, G.: A Facet of the Biohazard Control Program: Agent Registration, Risk Assessment and Computerization of Data. American Journal of Public Health. 66:4 372-374, 1976.

Karamian, N.A.: An Apparatus for Continuous Production of High-Purity, Bacteria-Free and Endotoxin-Free Water for Biomedical Use. American Laboratory. 8:3 24-28, 1976.

RADIATION SAFETY BRANCH

Michael B. Musachio, Chief

A. Objectives

Branch activities are planned to assure compliance with Part 10, Code of Federal Regulations, Chapters 19 and 20, conditions of the various licenses granted by the Nuclear Regulatory Commission, other applicable Federal regulations, and all policies established by DHEW and NIH in regard to the safe use of ionizing radiation. The Branch assists the NIH researcher in obtaining maximum benefit from the use of ionizing radiation while maintaining personnel exposure and the release of radioactive materials to unrestricted areas as low as reasonably achievable.

B. Current Programs

1. License Activities

Seven licenses issued to NIH by the Nuclear Regulatroy Commission permit the receipt, storage, use, and disposal of radioactive materials in accordance with NRC regulations and standards. License applications, renewals, or amendments are prepared and submitted to NRC as necessary. A semiannual inventory is conducted of all radioactive materials on the reservation to ensure that the possession limits prescribed by the NRC are not exceeded.

2. Radionuclide Shipping and Receiving

All incoming shipments of radioactive materials are checked for contamination, proper labelling and packaging, damage, and correct compound, isotope, and activity. A check is made as to whether the ordering individual is authorized by the Radiation Committee to receive the radioactive materials.

3. Radioactive Waste Disposal

The Branch is responsible for radioactive waste pick up, processing, assaying, packaging, disposal, and the keeping of waste disposal records in accord with Nuclear Regulatory Commission License conditions.

4. Patient Therapies and Diagnostic Studies

Health physics support is provided to patients receiving therapeutic doses of radioactive materials and in some diagnostic studies, to ensure proper dosage and that personnel exposures are maintained as far below permissible levels as is practical.

5. Radiation Safety Surveillance

Routine surveys are conducted in all laboratories where radioactive materials or equipment capable of producing ionizing radiation are used. The areas are surveyed for compliance with the provisions of 10 CFR 19, 10 CFR 20, Occupational Safety and Health Act, and other policies and standards approved or promulgated by the Radiation Committee. Appropriate followups are conducted, if necessary, to secure regulatory compliance. In the case of repeated noncompliance or highly hazardous conditions, the matter is referred to the Radiation Committee for appropriate corrective action.

6. Personnel Monitoring

Monitoring consists of film and thermoluminescent dosimetry for external radiation, and whole body counts and radioassays of urine samples for internally deposited radionuclides. Detailed lifetime exposure histories of all NIH employees are kept with periodic review and distribution of the results.

7. Training

Training activities are aimed at making all radiation workers fully aware of the regulations and policies governing the safe use of ionizing radiation, and cognizant of the hazards associated with its use.

8. Technical Assistance and Other Radiation Safety Services

Space, equipment, and health physics assistance is provided in Building 21 for the handling of high levels of activity not normally permitted in a typical NIH research laboratory. Shielding materials and portable survey meters are also provided to the laboratories. The survey meters are calibrated semi-annually as required by license condition and repair as needed. Technical assistance is given to the researcher in regard to effectively utilizing ionizing radiation in the conduct of biomedical research. Supervision and assistance is also provided in contaminating accidents. Increasingly, requests for technical assistance are received from NIH field stations, other components of DHEW, other federal agencies, state and local governments, universities, business organizations, and conquered citizens regarding radiation safety.

C. Program Progress and Accomplishments

1. License Administration

Two representatives of the Nuclear Regulatory Commission conducted an inspection of NIH activities authorized by Licenses 19-00296-10, 19-00296-11, and 19-00296-17 on February 10-12, 1976. These activities were found to be in substantial compliance with NRC regulations. A violation was reported as a result of two incidents involving exposure to concentrations of I-125 in excess of the maximum permissible airborne levels. Both incidents were reported to the NRC in March and April, 1975 as required by 10 CFR 20 and appropriate steps were taken by the Radiation Safety Branch to minimize the possibility of a recurrence. The monitoring of radioiodine released from

Building 10 has not been able to proceed as a result of inordinate engineering delays in installing sampling taps on the exhaust duct risers and the installation of vacuum sources in the mechanical rooms. Routine review and renewal of authorizations has been held up for lack of clerical and health physics support. The NRC expects that both of these matters will be corrected to their satisfaction by the time of their next routine inspection. The NRC inspectors also suggested that individuals performing iodinations have thyroid counts on a monthly rather than quarterly schedule.

An application was prepared and submitted to the Nuclear Regulatory Commission for the renewal of the Co-60 teletherapy unit License No. 19-00296-16. The license was renewed on August 28, 1975 and expires on August 31, 1980.

Special Nuclear Material License, SNM 1345, was amended to permit human implantation of up to 10 Caratomic, C-100 series, nuclear-powered cardiac pacemakers, for the purpose of clinical evaluation. The Radiation Committee was informed of the relatively high radiation dose from the surface of the pacemakers as compared to units previously licensed. The estimated gamma and neutron emissions ranged from 44-132 Rem per year. The hazard from this surface dose rate was not considered unreasonable when compared to the expected reduction in surgical mortality as a result of less frequent pacemaker replacement.

License No. 10-00296-10 was amended as a result of the Radiation Committee's request for a waiver of some of the specific requirements of NRC Regulatory Guide 8.13, "Instruction Concerning Prenatal Radiation Exposure." The Committee's letter of intent was incorporated into License Condition No. 25 and commits NIH to:

A. 1) Distribute to all radiation workers information emphasizing the current NCRP recommendations relating to radiation exposure of fertile-age and pregnant women.

   2) Emphasize that it is NIH policy to follow these recommendations.

   3) Also provide radiation workers with reminders of the special radiosensitivity of the embryo and fetus, including copies of Guide 8.13.

B. Make available to all radiation workers the opportunity to attend review sessions (orally presented), during which the recommendations of Guide 8.13 would be presented.

C. Have records of attendance at past radiation safety courses serve in lieu of the signed statements recommended in Paragraph C Guide 8.13, for those who do not elect to attend such sessions.

Approximately 180 applications for the use of radioactive materials (NIH Form 465-1) were reviewed during the year and forwarded to the Radiation Committee with appropriate comments. One hundred and fifty-seven of the applications were approved by the Radiation Committee and authorization numbers assigned.

Past difficulties in maintaining airborne I-125 releases from Building 21 below the maximum permissible concentration have been largely eliminated. This was accomplished by the design and installation of custom-made activated charcoal adsorption units to serve the iodination hoods, and the installation of an enclosure equipped with a recirculatory activated charcoal adsorption unit in the radioiodine storage hood.

2. Radionuclide Receipt and Delivery

A total of 10,170 shipments of radioactive materials with a combined activity of 150.2 curies were received during the year. The number of shipments increased 11 percent over the past year and the total activity increased 22 percent. The dollar value of these materials was $1,644,746, a 25 percent increase over last year.

3. Radioactive Waste Disposal

During the year 53,198 trays of liquid scintillation vials, each containing 100 vials, were picked up, packaged and disposed of by burial under the terms of Contract No. 263-76C-085CC. This was a 25 percent increase over last year.

A total of 693 drums of radioactive liquid and solid waste (other than scintillation vials) were prepared for disposal by burial. The number of drums shipped was below the budget forecast due to the installation of a new compactor in October, 1975. The new compactor has a 50 percent higher compaction ratio, permitting an increase in the weight of solid waste that can be disposed of per drum. Since the charges for disposal are based on volume rather than weight, it has resulted in significant cost savings. Adjusting for the higher compaction ratio, the amount of waste was 29 percent more than last year.

4. Patient Therapies and Diagnostic Studies

Health physics support was provided to 33 patients receiving therapeutic levels of radioactive materials, a 57 percent increase over last fiscal year. Most of the therapies utilized I-131 and lesser numbers involved P-32 and H-3.

5. Laboratory Surveillance

A total of 6,970 radiation surveys were conducted during the year, a 32 percent increase over the previous year. The Institute for Resource Management conducted 1,822 routine compliance and contamination surveys under contract and Radiation Safety Branch personnel conducted 1,957 followup or special surveys for a combined total of 3,779 laboratory surveys. This was an increase of approximately 29 percent over the previous year but 27 percent less than the goal of at least 4,800 laboratory surveys per year stated in the license application. In addition, 3,024 air samples were collected to monitor the concentrations of various radionuclides in the work area and the environment, an increase of approximately 36 percent above last year. A contractor conducted 147 routine x-ray surveys and an additional 20 special and follow-up x-ray surveys were conducted by Branch personnel, a 7 percent increase over last year.

6. Personnel Monitoring

The processing of personnel dosimeters to evaluate radiation dose from external sources was provided under contract. The number of individuals on film badges increased from 1,945 last year to 2,127 (a 9.4 percent increase). In addition 227 employees were issued wrist badges and another 55 routinely wear finger dosimeters. Also, 43 employees of the Rocky Mountain Laboratory and two Arizona field stations are covered by the film badge contract.

An attempt was made to replace the Radiation Safety Branch thermoluminescent wrist dosimeter with a commercial model. Originally designed for use in the Heart Catheterization Laboratory, the RSB dosimeter has found wide acceptance in Diagnostic Radiology, Nuclear Medicine Department, and Radiopharmacy Section. As a result of poor acceptance of the commercial dosimeter, however, it became necessary to resume issuing the RSB model.

The number of radioassays of urine obtained from individuals working with beta emitting radionuclides increased from 1,260 last year to 1,369, an increase of 8.7 percent.

Whole Body counts were requested for 579 authorized users and their employees who worked with established levels of gamma emitting radionuclides. This was a 35 percent increase over the previous year and resulted in 2,446 in vivo measurements being conducted by the Whole Body Counting Section, NM,CC. As a result of the most recent Nuclear Regulatory Commission inspection, it is expected that the number of whole body counts will increase approximately 100 percent.

7. Radiation Safety Training

Radiation safety training activities over the year focused upon continued training of new users of radiation sources in the NIH clinical and research efforts. This involved presentation of the courses and training sessions noted below in which approximately 1,756 man-days of training were received by some 1,177 NIH staff members. In addition, 44 visitors from other agencies and private laboratories attended the one-day session, "Radiation Safety in the Laboratory."

A major effort was put forth in March, 1976 in presenting a formal radiation safety review for those authorized prior to the Spring of 1973. This session, 90 minutes in length, concentrated on addressing 1) an update on radiation safety problems of special concern to radionuclide users at the NIH and, 2) hazards and precautions relating to radiation exposure of pregnant women. These sessions served the dual purpose of meeting recommendations of the NRC regulatory Guide 8.13, and a related newly-imposed condition on NIH's Broad NRC License. As summarized below, 295 of the approximately 500 active Authorized Users authorized prior to Spring, 1973 attended these sessions. One hour sessions reviewing "Radiation Exposure of Fertile Aged and Pregnant Women" were made available for those who attended Radiation Safety Branch sponsored courses since Spring, 1973.

Radiation Safety Review for Authorized Users

Date Presented		Attendance Authorized Users	Others
March 3		99	15
March 8		95	22
March 16		101	16
	Total	295	53

Radiation Exposure of Fertile Aged and Pregnant Women

Date		Attendance
March 5		25
March 11		15
March 18		20
	Total	60

Ongoing radiation safety training activities include the presentation twice yearly of the 2-week course, "Radiological Health for Radionuclide Users." This course, or equivalent training, is prerequisite to becoming an Authorized User under NIH's Broad NRC License, both for clinical and laboratory use of radionuclides.

A second course, "Radiation Safety in the Laboratory," of one day duration, was presented ten times during the past year. Attendance of this course is required for all radionuclide users who do not fall into the Authorized User category.

Radiation Safety in the Laboratory

Date		Attendance NIH Staff	Visitors
July 8		42	
August 7		75	11
September 26		59	9
October 20		47	1
December 16		33	1
January 20		29	3
February 24		21	7
March 24		50	4
April 23		28	7
May 20		32	1
	Total	416	44

Other training activities relate to presentation of specialized sessions for NIH staff who may encounter radiation sources in their work. One hour sessions were presented to nurses as part of their orientation to the Clinical Center on a monthly basis during the year, with a total of 144 nurses in attendance. A one hour review session was presented to 34 nurses as part of their in-service training. A specialized session was presented to seven nurses, who work with patients who have large amounts of radioiodine administered for therapeutic purposes. Lastly, a one-hour session was presented to 45 members of the Clinical Center housekeeping staff.

8. Technical Assistance

Special surveys were conducted in the Nuclear Medicine Department, CC, to assist in upgrading the radionuclide storage and dosing area and to improve the ventilation system in the room used for Xe-127 and Xe-133 studies.

Health physics assistance was provided to the Nuclear Medicine Department, CC, to evaluate the hazards of Xe-127 and assist in the development of techniques for the safe fractionation of bulk shipments of Xe-127 into 8-10 millicurie unit doses.

Technical assistance was given to the Clinical Center for the development of their Hospital Disaster Plan, particularly, as it related to a radiation accident.

A review was made of the suggested model State and Federal Regulations for the Control of Radiation. Comments were forwarded to the Bureau of Radiological Health, FDA, which is coordinating publication of the model code.

A new bromination procedure was developed in cooperation with an NIH investigator. The new procedure has a considerably higher labelling efficiency than the previously used one and significantly reduces the radiation hazard to personnel.

At the request of the Acting Chief, Phoenix Clinical Research Section, NIAMDD, a survey was conducted to evaluate radioactive material handling and disposal procedures, particularly as they related to I-125. A summary of the findings and recommendations were made orally before leaving the facility and a written report followed shortly.

NIH tantalum and tungsten syringe shields were developed as a result of Nuclear Medicine personnel's dissatisfaction with commercially available shields. The syringe was developed jointly by Nuclear Medicine Department, CC, Radiation Safety Branch, and the Biomedical Engineering and Instrumentation Branch, DRS. The routine use of the syringe for dosing nuclear medicine patients has resulted in more than 200-fold reduction in exposure to the skin on the fingers and hands of dosing personnel. A bronze clad depleted uranium shield was developed for Ga-67 administration. All of these shields are now available commercially at a reasonable cost and it is felt that their development is a significant contribution to radiation safety.

Technical assistance was provided to several hospitals, universities, other Federal agencies, commercial firms, and concerned citizens regarding radiation safety problems. Most of the inquiries of private citizens were in regard to medical and dental x-rays; other requests for assistance were in regard to I-125 air sampling and control measures.

The high level radioisotope laboratories in Building 21 were used by approximately 500 investigators during the year, a 9 percent decrease from last year which had increased 112 percent above the previous year. The decrease is due primarily to the installation of the RSB-developed iodine containment hood in a number of laboratories and to a much lesser extent due to the increasing number of complex procedures, approved by the Radiation Committee, which cannot be readily accomplished in Building 21. The greater number of high level experiments conducted outside of Building 21 puts an additional workload on the health physics staff.

D. Problems

The most critical problem facing the Radiation Safety Branch continues to be the rapid increase in the use of radioactive materials in the NIH intramural research program. Current manpower resources are inadequate to maintain a desirable level of health physics services and to assure compliance with the provisions of 10 CFR 19, 10 CFR 20, License Conditions, and Occupational Safety and Health Act requirements.

This situation was reported to the Director, NIH, in 1968 and again in 1975 by the Radiation Committee. The Radiation Safety program is caught between rising radionuclide usage and increasingly more stringent regulatory requirements. Over this period of time the work force has remained static. In order to cope with the situation the Branch has resorted to more contracting, part time personnel, and increased overtime. Program priorities have been reevaluated, the program reorganized, personnel reassigned, and increased responsibility placed on the authorized user. As a result of these actions and the strong support of Radiation Committee there has been a significant improvement in the level of compliance with radiation safety requirements at NIH.

However, gains made up to this time are being offset by increased regulatory requirements and the continued increase in the use of radioactive materials at NIH. The program activity most visibly affected is the radioactive waste pickup and disposal service. The volume of waste has increased at a rate of approximately 30 percent over the past several years. As a result there has been a serious deterioration in the level of service provided to the laboratories and the situation in the Building 21 waste processing area is acute. To alleviate the situation, this program activity will be serviced by contract, effective April 1, 1976.

During past inspections, the Nuclear Regulatory Commission indicated a need for tighter administrative control over radionuclide authorizations. It was felt that all authorizations should have a 3-5 year expiration date, specify radionuclides to be used, activity, chemical and/or physical form, intended use, location of use, etc. Plans for such a program were not implemented as a result of higher priority activities competing for the limited personnel resources. At the most recent NRC inspection the matter was again noted in the inspection report and NIH is obligated to take corrective action if a citation is to be avoided.

It has been recognized for several years that there is a need to monitor the radioactive effluents from the various NIH buildings in a more effective manner. The NRC is becoming increasingly aware of this situation, particularly in regard to monitoring I-125 in effluent air, and commented on it during the last inspection. The air monitoring program for Building 21 is good. However, the exhaust air from the other buildings is sampled only twice a year by the collection of grab samples, which is inadequate. In addition, there is a need for routine waste water monitoring. Previous attempts at such sampling indicate it is difficult and complex, requiring a considerable expenditure of time and money.

The rapid increase in the use of radioimmunoassay procedures utilizing I-125, requires increasingly higher levels of surveillance as a result of NRC's concern over the hazards. During the most recent NRC inspection it was recommended that persons performing iodinations have monthly, instead of quarterly, thyroid counts, as is the current practice. It is anticipated that this will increase the number of _in vivo_ counts by at least 100 percent. Furthermore, it is anticipated that more stringent guidelines for bioassay sampling will be imposed by the Nuclear Regulatory Commission. Any such action will also impose a significant increase in the Branch workload.

Training is a key component of an effective radiation safety program. Although the level and quality of radiation safety training at NIH is high by most standards, there is a need to expand the program in the following areas: continuing education of authorized users, x-ray technologist training, more frequent presentation of the "Radiological Health for Radionuclide Users" course, and training of such groups as firemen, guards, Employee Health Service personnel, nurses, custodians, shop personnel, etc. There is also a need for a more effective multi-media campaign consisting of films, video tape, slides, posters, news articles, informative memoranda, etc., to aid in the dissemination of radiation safety information and to reinforce previous training. There has been substantial community demand for the NIH sponsored radiation safety courses as a result of word of mouth dissemination of scheduled training dates. Resources are not currently available to implement a radiation safety training program of the magnitude and quality that is deemed necessary to alert radiation workers of the potential hazards, familiarize them with the techniques for minimizing exposure, and to motivate them to comply with accepted radiation practices.

The requirements for off-site use of radioactive materials and radiation producing devices by NIH staff members are outlined in the NIH Radiation Safety Guide and PPM 1344. The Radiation Committee recently reaffirmed this policy. The number of individuals working off-site has increased at a very rapid rate in recent years, particularly NCI. Due to more immediate problems on the reservation, difficulty in identifying these individuals and their location, and limited resources, this policy has not received the attention it deserves.

E. Program Plans

Highest priority will be given to improve work procedures and the optimum utilization of available resources. The further use of contract services and positions not counting against the personnel ceiling will continue to be explored. Existing contracts will be monitored to assure high quality service at an economical cost and program activities will continue to be reviewed to identify areas that readily lend themselves to contracting.

Continued high priority will be given to Radiation Safety training as required by 10 CFR 19. Technician training will stay on a monthly basis, and attempts will be made to develop and present an x-ray technician training program. A continuing education course for Authorized Radionuclide Users will be developed and presented on a routine basis. It would be desirable to increase the frequency of the two week course "Radiological Health for Radionuclide Users" to three times per year so as to partially offset the high demand for such training. However, it cannot be attempted at the current level of staffing.

The level of surveillance will be increased, particularly in laboratories utilizing radioactive materials, thyroid counting of radioiodine workers, and the routine monitoring of effluent air for I-125.

A program for the routine review and renewal of radionuclide authorizations must be implemented prior to the next Nuclear Regulatory Commission inspection.

Continued support will be provided to the Equal Employment Opportunity Program and the DRS and RSB Human Relations Committee activities.

F. Publications

Hence, A., Crystal, R., Wagner, W., et al.: Biochemical Approaches to Investigation of Fibrotic Lung Disease. Chest, 69:2 (Suppl) 1976.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities — July 1, 1975, through June 30, 1976

LIBRARY BRANCH — Ruth C. Smith, Chief

I. SUMMARY

The Library Advisory Committee met several times during the year. Dr. Joe R. Held served as temporary chairman, replacing Dr. Philip B. McMaster, NIAID, until March when a new chairman, Dr. Ann L. Sandberg, NIDR, was selected.

Preparations continued toward installation of the Automated Circulation Control System which will provide more effective service and control of books and journals loaned to NIH staff. Conversion of bibliographic book and NIH user records into computer data files has been completed.

A Scope and Coverage Policy for the NIH Library was completed by the Library staff and became effective as a guide for selecting literature for the Library's collection.

A job restructuring program was developed for the establishment of two career ladders whereby qualified Library Technicians could progress in a planned program of on-the-job and academic training from a nonprofessional GS-series to a professional position of Technical Information Specialist. The program provides for a planned progression of positions toward one target position in each of the two Units of the Technical Services Section and includes position descriptions and outside training programs for each position. Initiated in 1973, this project was reactivated in 1975 after the reorganization of the Section.

Newer terminals were installed to speed bibliographic retrieval services for investigators via MEDLINE (Medical Literature Analysis and Retrieval System On-Line) and the new TOXLINE (Toxicology Information On-Line) data bases at the National Library of Medicine.

The Library's literature in nonprint form has been organized in a central area and a modest number of audiotapes and videocassettes have been acquired.

A new Librarian position was created in the Office of the Chief to provide staff assistance in the area of technical services. This position was substituted for a similar position in the area of readers services which was vacated by retirement.

The Branch Training Program for all staff members contributed improved service to NIH staff, increased pertinent knowledges and skills for Library staff and provided more effective employee utilization.

Exhibits prepared by the Library staff include displays of the computerized bibliographic retrieval services of the Library, historical books in the collection, NIH Minority Cultural Week celebrations, National Library week, and services of the DRS Biomedical Engineering and Instrumentation Branch.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive library in support of NIH scientific, medical, and administrative programs. Activities of the Library include selection, acquisition, organization, maintenance, and circulation of literature pertinent to the programs; operation of a photocopy service; provision of interlibrary loan service; provision of informational, reference, and bibliographic services; provision of Library services advisory assistance; and provision of a translating service for foreign scientific and medical literature. To fulfill its mission, the Library is responsive to changing literature needs of the NIH investigators, is knowledgeable of current developments in manual and machine methods of communication and information retrieval, and is alert to adjustment of procedures for improved Library services.

B. Current Programs

Technical Services

The Journals Processing staff procures journals by purchase, gift, and exchange which have been selected as pertinent to the scope of the Library. The staff organizes and processes the journals for inclusion in the collection and maintains accession records using manual and automated systems. It also prepares completed volumes for commercial binding.

The Monographs Processing staff procures monographs and similar literature which have been selected as pertinent to the scope of the Library. The staff catalogs, analyzes for subject representation, and processes these accessions for inclusion in the collection. Both manual and automated systems are used. It also maintains the Library's catalogs and prepares listings of additions to the Library's collection for the Librarian's monthly memorandum.

Readers Services

The Circulation staff maintains a charging system, and issues Library Identification Cards; operates the Library's security system; provides an overdue recall system; and makes assignments to locked study carrels.

The Stacks and Copy Service staff maintains the stacks, carrels, reference and Reading Room areas and shelves books and journals. A copy service is available for NIH researchers.

The Interlibrary Loan staff obtains literature from other libraries required by NIH investigators.

The Readers Services Section is responsible for developing, maintaining, and servicing a collection of library material in nonprint media pertinent to the scope of the Library and for providing equipment for its use.

Reference and Bibliographic Services

The Reference staff supplies ready response to questions, verifies citations, and compiles short reference lists upon request. The staff compiles literature searches upon request and maintains the currency of the collection of basic Reference Books. Bibliographic assistance is provided through medical, chemical and biological computer searches of the National Library of Medicine's MEDLINE, Chemical Abstract's Chemical and Biological Activities (CBAC), and Biological Abstract's BioSciences Information Service (BIOSIS). Library Services Advisers integrate resources and services available in and outside the NIH Library, such as specialized information centers, computerized information retrieval systems, and clearinghouses. Professional staff also selects pertinent literature to develop and supplement the Library collection.

Translating Service

The Translation staff provides oral, recorded and written translation as requested. Oral translations are emphasized in-Library. Written translation service is provided through contractual firms with quality control maintained by the Library.

C. Program Progress and Accomplishments

Technical Services

Participation in the Ohio College Library Center's (OCLC) automated shared cataloging network system has greatly reduced the time required to process materials for the collection. Complete access to most new materials in the public catalogs is now possible in 2 to 3 weeks as compared to 6 weeks when traditional cataloging methods were used.

Readers Services

Considerable shifting of the main journal collection on the Lower Level was necessary to relieve crowded stack conditions and later for the inclusion of the 1970 journals from the Last Five Years collection on the Upper Level. Transference of certain abstracts and indexes from the Upper to the Lower Level was also necessary to provide shelving space for recent issues.

Progress continued on preparations for introduction of an Automated Circulation Control System which will provide more effective service and control of books and journals loaned to NIH staff. The system used by the University of South Carolina Library was modified by the Division of Computer Research and Technology to meet the needs of the NIH Library. Bibliographic records for books and Library borrowers data were converted into computer files; a PDP 11/40 minicomputer and system equipment were installed in the Unit location. Remaining for completion are the conversion of bibliographic records for bound and unbound journals, the assignment of bar-codes and affixing of bar-coded labels to each issue and volume in the collection and to each Library Identification Card, further instruction for the Circulation Unit staff, and program and system testings.

Interested librarians and other persons from governmental and other agencies have visited the Section to learn of the Automated Circulation Control System. Presentations on the system were made by Library staff to librarians attending the October annual meeting of the Mid-Atlantic Regional Group, Medical Library Association held in Morgantown, West Virginia, and to DRS employees attending the DRS Expanded Staff Meeting in January.

The Library's literature in nonprint form was organized in a central area and a modest number of audiotapes and videocassettes have been acquired. A Catalog of Audiovisual Materials in the collection has been prepared for publication.

Reference and Bibliographic Services

Guidelines for the selection of books, journals and other literature for the collection became available for use by the Library's selectors with completion of the Scope and Coverage Policy for the NIH Library. The Policy defines the scope and range of subject areas and indicates the depth of coverage for subjects collected.

New computer terminals are giving NIH investigators a more effective bibliographic retrieval service through access to MEDLINE (Medical Literature Analysis and Retrieval System On-Line) data bases at the National Library of Medicine.

The number of completed MEDLINE bibliographic search requests continued to increase in calendar year 1975 with a total of 8842 searches, representing an increase of 1622 searches (22%) over the number performed in 1974. Current awareness searches included 206 profiles for BIOSIS Previews (Biological Abstracts), 41 for CBAC (Chemical-Biological Activities) and 138 for SDILINE (MEDLINE's Selective Dissemination of Information On-Line).

Translating Service

The Translation service continued at the same level with approximately 1450 requests. Of these, 400 were for oral in-Library translations and the remainder for written translations. Existing translations were located to fill 400 requests, and 650 requests, which represented over 2 million words, were met through contractual service.

Training

The FY 76 Branch Training Program provided individual employee training in academic, professional, governmental, administrative and technical courses and in-Library lectures to promote employee development. Long-term training was continued by three employees in the Adult Education program (two in the regular program and one in a special training course), by four employees enrolled in the NIH/Federal City College Upward Mobility College, and by one employee at the University of Maryland.

Exhibits

Exhibits displayed during the year covered the following topics: Biomedical Engineering and Instrumentation Branch Services (prepared by BEIB); CANCERLINE Bibliographic Service; Asian-American Cultural Week; Black History Week; National Library Week; Retrieval of Technical Reports; and Bibliographic Services offered by the NIH Library. Art assistance was received from the Medical Arts and Photography Branch.

D. Problems

Additional space will be one of the major problems in the Library in the near future, especially for the journals stacks area. Presently there is room for two annual moves of journals from the Upper to the Lower Level. Consideration needs to be given to: weeding the journal collection; provision of nearby storage space for convenient access; elimination of most second journal subscriptions; replacement of hard copy by microform; or expansion to the third level of the Library Building which was constructed to meet future requirements.

A move to the third level also would help to alleviate a space problem in the Technical Services Section. At this time, as a temporary measure, furniture of a smaller scale will provide additional work space for the staff of this Section.

E. Program Plans

Implementation of the Automated Circulation Control System will improve the effectiveness of the services relating to loans and overdues and will provide inventory control of the collection.

Plans will be developed for the conversion to the medical subject heading system (MESH) of the National Library of Medicine for the medical part of the Library's collection. Specialized terminology in the Library's catalogs will provide the NIH staff a more responsive index for identifying and locating medical books, journals and other literature in the collection.

With the assistance of staff of the Division of Computer Research and Technology, the possibility of a total automated library system based on the minicomputer will be investigated. Implementation of such a system would be made in modules related to specific library functions, such as acquisitions, serials, and interlibrary loan.

Specific plans to upgrade the monographs collection in conformity with the newly developed Scope and Coverage Policy will be made with the assistance of the Library Advisory Committee.

F. Publications

National Institutes of Health Library: Memorandum: Recent Additions to the NIH Library. Monthly (Internal Use Only)

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1975 through June 30, 1976

MEDICAL ARTS & PHOTOGRAPHY BRANCH Mr. Arthur F. Moore, Chief

I. SUMMARY

Demand for MAPB services increased approximately 10 percent in FY 1976. The larger workload was met by a corresponding increase in contracted services. Delivery of finished art work was accelerated and delivery of normal photographic service was reduced from seven to five work days. Establishment of graphic standards for statistical materials produced by the Branch was completed. This is the first phase of a continuing effort to establish a unified visual communications system for the NIH. With new equipment, wider use of contract services and training, the Branch continued to broaden its skills and meet increasing demands for services.

II. BRANCH PROGRAMS

A. Objectives

The objectives of the Branch are to provide consultation and production services to the NIH; to visually communicate program efforts and research results; to provide knowledge, skills and techniques in visual design, medical art, applied arts, still photography, and cinematography for solving problems of recording, communicating, and presenting research activity; and to investigate, develop, and upgrade visual techniques.

In meeting NIH research program demands, the Branch provides professional services competitive with commercially obtainable services at the lowest possible cost. It develops specialized capabilities, particularly in graphic presentation, still photography, cinematography, and medical arts that are tailored to NIH needs.

The Branch monitors art and photography services procured by outside contract, serving as a technical adviser to obtaining needed additional services at the lowest cost consistent with high quality.

B. Current Programs

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, cine photomicrography, high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design, and general graphics; visual aids including slides, vu-graphs, and other projectables; animation artwork; technical, general, and medical illustration; exhibit design; statistical drafting display charts, and medical models.

C. Program Progress and Accomplishments

Much of the increased demands for MAPB services were caused by Federation Meetings, the second NIH Public Open House, and the Bicentennial celebration.

An extensive DRS study revealed the Graphics Unit of the Design Graphics Section to be a service ideally suited for financing by the NIH Service and Supply Fund. When this new service is approved, it will mean faster delivery to the NIH requester and greatly improve manpower use in the area.

In its continuing efforts to upgrade visual communications, the Branch hired a design consultant to survey the diagramming processes of NIH, make recommendations, and develop the first phase of a design manual. A design manual is needed to provide uniformity of graphic quality, improve communications, and to effect economies by establishing standards and that will help eliminate preliminary design problems.

Older photographic equipment was replaced with new equipment, enabling the Branch to increase production, shorten response time, and improve the quality of finished photography. The average in-house time to complete a job was reduced to five work days. Of the 25,728 jobs completed in FY 1976, 27 percent were done on a rush basis of less than five work days. Some of the work was completed on the same day to honor emergency requests.

Requests for medical illustrations remained normal in FY 1976, with a minimal number of projects on short deadlines put out on contract.

MAPB personnel spent 1,544 hours in 32 training courses at a cost of $4,293.00.

The Branch renewed without change the two-year negotiated agreement with AFGE Local 2419. Relations have been smooth and without incident.

An ongoing program to familiarize Branch employees with Equal Employment Opportunity goals and all aspects of the merit promotion plan continued.

D. Problems

There remains a critical need for the NIH community to allow more reasonable lead time for planning and execution of audio-visual materials. All too often, the thoughtless and needless demands for rush work deprive the majority of NIH requesters the service they deserve. The Branch has extensive expertise in planning and conversion of raw data into effective multi-medial presentations. This counsel is readily available in all areas of MAPB, or on location, and should be used earlier and more frequently.

E. Program Plans

The Medical Arts & Photography Branch will pursue the development and implementation of a system to upgrade NIH visual communications. It will continue to improve, enlarge and extend its services and will seek more effective ways to acquaint the NIH community with its skills. The Branch will continue to emphasize the need for early counsel and planning to provide optimum services.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1975 through June 30, 1976

VETERINARY RESOURCES BRANCH Dr. Robert A. Whitney, Jr., Chief

I. SUMMARY

The Veterinary Resources Branch provides NIH investigators with living animal models and biological products for medical research. The Branch also provides collaborative research, facilities, and services related to the use of these models and products.

VRB service functions continued to increase in FY 1976 to meet demands of expanding intramural BID programs, although Branch personnel ceilings have been reduced over the last several years. Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, limited use of temporary positions, and contracting.

In February 1976, Branch activities were reduced in scope to include only veterinary programs with the transfer of the Media and Glassware Section from VRB to the Environmental Safety Branch, DRS.

Total issues of VRB-produced, small animals remained at about 500,000. Inbred mouse production increased slightly over last year despite two problems which necessitated phasing out some production colonies and reestablishing them. The colonies in question were affected by a Sendai virus contamination and a genetic contamination.

Extensive testing for genetic integrity was performed on the foundation colonies of BALB/c. A/HeN, and AKR/N mice following the discovery of genetic compromise in the production colonies. Skin grafting, test mating, mixed lymphocyte cultures, and biochemical tests were performed. All indicated the foundation colonies were unaffected, allowing reestablishment of the production colonies.

Contract-purchased small animals increased from about 84,000 animals last year to about 150,000 this year. New contracts were established for Hartley guinea pigs and inbred mice and rats.

The VRB genetic repository of small animals supplied more breeding nuclei to establish new colonies outside NIH than in any previous year. All major National Cancer Institute small animal contract programs are now relying on VRB as the genetic base for their colonies. Germfree and pathogen-free snimals were provided as pedigreed nuclei for the Frederick Cancer Research Center and other Division of Cancer Treatment and Division of Cancer Cause and Prevention contractors. This is the first year DCT has utilized this resource.

Barrier maintained mouse and rat colonies are now being fed a new open formula autoclave ration containing 18 percent protein instead of a 24 percent commercial ration. The ration, developed by the VRB nutritionist, is expected to result in a 25 percent saving.

The Experimental Surgery Unit of the Veterinary Medicine and Surgery Section (VMSS) was relocated from Building 28 to Building 14E. The new location permits more surgical and support space and planned renovations will increase considerably the quality and quantity of centralized surgical support available to the Institutes. Renovations to Building 14D continued throughout the year with completion due in the fall of 1976. Complete renovation of this facility will create a holding capacity for over 1,800 nonhuman primates for infectious disease and other intramural programs. The VMSS has increased its participation in collaborative research projects within the Institutes. A large-scale collaborative project with the National Heart and Lung Institute (NHLI) on atherosclerosis in miniature swine was successfully completed in FY 1976.

Renovations were started in the indoor/outdoor animal holding facilities of Building 28. More than 3,000 rhesus monkeys were quarantined and issued with over 550 going to NIH intramural breeding programs. Contract programs with Gulf South Research Institute, Hazleton Research Laboratories, and the Perrine Primate Center reached projected breeder capacity with a total of over 1,500 breeding rhesus monkeys.

The Animal Disease Investigation Service experienced a 59 percent increase in the number of calls over the previous year. This service continues to be mutually beneficial to BID investigators and to the VRB professional staff.

Written SOP's on VRB quality assurance programs for a wide variety of products and programs were prepared. They included microbiological and genetic monitoring and disease surveillance of small and large animals, environmental monitoring, and employee health.

NIH utilization of dogs was the lowest of any year on record, declining 26 percent from fiscal 1975. The breeding of larger animals such as goats and burros increased in scope, as did the breeding of purebred foxhounds at the Animal Center Section. No random source dogs were used. Contract production of purebred foxhounds will continue. The creation of outdoor housing space for growing puppies is expected to be completed in the year and will permit purebred production to expand by 200 to 300 pups per year. Improvement of the lease property at the Animal Center Section, consisting of some 200 acres of pastures and several buildings adjacent to the Center, will provide more space for sheep, swine, and burros. Expansion of swine breeding/holding activity is anticipated early in FY 1977 with erection of a temporary farrow/holding structure on the leased property.

A computerized recordkeeping system is being developed by VRB for use in small animal breeding, colony management, and in the collection of pathology and clinical data on primates used in research.

II. BRANCH PROGRAMS

A. Objectives

1. Animal Center Section

The Animal Center Section produces, procures, and issues large research animals. Facilities and ancillary personnel are provided for experimental surgery on ungulate animals, including supportive postoperative care, radiographic, and other special procedures. Animal biological products are produced and issued. Information is developed through research to improve animal health, husbandry, and medical care. Animal models for human diseases are developed through collaborative research.

2. Comparative Pathology Section

Studies of naturally-occurring diseases of laboratory animals are made to characterize and improve their health status.

3. Small Animal Section

Laboratory animals are issued for NIH intramural research. The Section maintains a centralized genetic repository of valued animal strains for the national and international scientific communities; maintains animals during gnotobiotic experimentation and collaborative research support; acquires information, through independent research, on animal health, care, and husbandry and identification of animal models for human disease. The Section also provides consultative services on animal health and husbandry and use of experimental animals; establishes and supervises production colonies of animals that are not commercially available to the NIH community; monitors procurement of animals and environmental conditions.

4. Veterinary Medicine and Surgery Section

The Surgery Unit provides a complete program for BID investigators for experimental surgery on research animals. The Comparative Medicine Unit provides holding and care for dogs, cats, miniature swine, sheep, goats, and other of the larger species of animals for research purposes. The Primate Research Unit provides for timed pregnant breeding and holding nonhuman primates assigned to research projects.

B. Current Programs

Animal Center Section

1. Animal production--Goats and blood group CEA 1, 2 and 3 negative foxhounds are produced in breeding herds and colonies.

2. Animal procurement and conditioning--Nonhuman primates, cats, ungulates, and feral animals are purchased and conditioned. These animals are not well defined genetically or microbiologically. Although they are of lower quality than NIH-bred animals, they are satisfactory for certain studies. These

animals are quarantined prior to release for use in research programs. During the quarantine period they are given appropriate immunizations, tested for a variety of infectious agents, and are treated medically as required.

3. Animal biologics production--A colony of blood group CEA 1, 2, and 3 negative canine donors is maintained for the production of normal canine blood for research use. Ungulate animals are maintained for the production of antisera, normal blood, or tissue specimens.

4. Experimental surgery and radiographic activities--Facilities are provided for investigators to perform experimental surgery on ungulate animals. They include modern equipment for restraint, anesthesia, and physiologic monitoring under aseptic conditions. Postoperative care is provided and radiographic facilities are available.

5. Animal holding--Ungulates are held under observation for NIH investigators during investigative studies. Physiological sampling and specimen collections are provided in association with these studies. Research holding facilities also are provided for the long-term observation of dogs.

Comparative Pathology Section

Laboratory animal disease diagnosis is performed by a staff of pathologists and microbiologists to aid in the control and elimination of disease in NIH animal colonies. Disease problems are dealt with in a wide variety of animals in conventional, germfree, and barrier-sustained colonies. Monitoring for the presence of a wide variety of microbiological agents and parasites is performed routinely. Research is conducted on the pathogenesis of naturally occurring diseases of laboratory animals to facilitate both diagnosis and control of such diseases. Laboratory assistance, training and administrative liaison are provided for animal disease investigators concerned with the control of diseases in NIH research laboratories. Tissue processing services also are provided.

Small Animal Section

1. Research animal production--Rodents and rabbits are bred and reared in colonies. Some are characterized genetically and some are microbiologically defined. Care is taken to maintain the genetic integrity of inbred strains and to minimize inbreeding or random bred stocks. Germfree and specific pathogen-free (SPF) rodents are produced for intramural research programs requiring them for replacement breeders to enhance the health status of production and genetic colonies.

2. Research animal procurement and conditioning--Rodents and rabbits are procured through contracts to augment in-house production. They are delivered directly to NIH investigators. Quality control of these species is maintained through monitoring of the various producers' facilities and operations by Branch staff members.

3. Genetic repository and new animal models program--Genetically defined rodents that are valuable models in biomedical research are derived, defined, and maintained to support BID requirements and serve as a genetic repository for the international scientific community.

4. Experimental animal holding--Germfree rodents are held for varying periods of observation while under test by NIH investigators. Provision is made for physiological sampling and collection of specimens.

5. Disease investigation, research, and quality control--The SAS professional staff consists of persons trained in general clinical veterinary medicine and specialists in laboratory animal medicine, epidemiology, nutrition, genetics, and animal husbandry. All efforts are oriented toward improving the section's programs by gaining new knowledge through research and monitoring the quality of procured and produced animals.

6. Consultative services--Information and assistance are available to NIH investigators for solving problems relating to animal experimentation, health, care, and husbandry.

Veterinary Medicine and Surgery Section

1. Surgery Unit--This unit provides a complete program for BID investigators for experimental surgery on research animals. The facilities include equipment for anesthesia, physiological monitoring, radiology, and surgical support to assure humane and aseptic technique to the laboratory animals. Upon request, staff veterinarians will perform service surgery on animals or collaborate in the preparation of animal models. Consultation in developing research protocols is provided. Complete veterinary care is provided, including pre and postoperative medical care for all research animals.

2. Comparative Medicine Unit--This unit holds and cares for dogs, cats, miniature swine, sheep, goats, and other of the larger species of animals for research purposes. Collaborative studies include development of animal models for human diseases not requiring surgical procedures. Veterinary medical support and consultation are provided.

3. Primate Research Unit--This unit provides for timed pregnant breeding and holding nonhuman primates assigned to research projects. It makes available investigator work areas, complete veterinary care, and research support with technical assistance and professional collaboration. A breeding colony of rhesus monkeys and baboons is maintained to provide timed pregnant females or neonates as requested by BID investigators for research protocol requirements.

C. Program Progress and Accomplishments

1. Animal Center Section

The conventional canine breeding colony consists of 118 bitches and 14 dogs. Culling continued to eliminate poor producers and animals with hip dysplasia. The inbred foxhound colony consists of one English and two American (Walker) strain foxhound lines. Two lines attained the second generation and one line reached the third generation of inbreeding. Development of these lines is directed at providing a genetically uniform research dog for NIH investigators by eventually crossbreeding the lines.

Approximately 750 purebred foxhounds were supplied by a contractor for NIH research. Availability of purebred stock from NIHAC and contract sources has alleviated the need to rely upon random source foxhounds and eliminated the need for random source mongrel dogs as standard NIH research animals.

The goat breeding herd was expanded from 20 to 30 does and to 2 bucks. Goats produced from the breeding herd are held until approximately 1 year old before issue.

Requests for random source cats appear to be stable. Projected issues were approximately 800.

Approximately 667 ungulate animals were purchased, quarantined, conditioned, and issued during the year. In addition, some 78 domestic fowl, including ducks, chickens, and turkeys were used. These figures represent increases of 28 to 35 percent.

Rhesus (*Macaca mulatta*) monkey issues were estimated at about 3,100, which represents a decrease of about 900. This is related to reduced availability of rhesus monkeys because of Indian export quotas and decreased requirements for contract breeding stock.

This year, 548 rhesus monkeys were quarantined, selected, and delivered to Gulf South Research Institute, Hazleton Laboratories, and Perrine Primate Center to completely satisfy requirements for contract breeders.

Cynomolgus monkeys (*M. fascicularis*) were made available for NIH researchers to evaluate as a possible substitute for rhesus monkeys. Approximately 330 cynomolgus monkeys were issued.

Other species of monkeys and apes (*M. arctoides*, *Erythrocebus patas*, *Saimiri sciureus*, *Cercopithecus aethiops*, *Aotus trivirgatus*, and *Callithrix* sp) contributed small numbers to the overall quarantine and conditioning program.

Space was made available to house research dogs on a long-term basis. Approximately 80 experimental dogs are maintained on a continuing basis. The number of livestock produced by breeding herds that were held for investigative purposes, quarantine, or during transit between contract and laboratory facilities increased from 610 to 720.

Domestic turkeys, chickens, and ducks were used at a greater rate this fiscal year to produce normal blood and antisera for specific research projects. The 234 dogs in the canine blood donor colony produced an estimated 3,400 units of blood (1 unit = 500 ml).

Biologics production from ungulate animals, slightly less than last year, was projected at 1,200 liters.

Activities in ungulate surgery declined. Surgery was used for porcine skin transplantations. Miniature swine breeding continued to develop four inbred lines of immunologically distinct animals. Eight sows have produced 47 progeny.

Radiographic procedures increased from 320 exposures in FY 1975 to 455 this fiscal year. The increase was largely attributable to the use of portable units acquired for diagnostic purposes in primate quarantine and canine breeding activities.

Fecal culturing for Mycobacterium paratuberculosis in the goat herd continued. The incidence of Johne's disease was 12 in 1972, 2 in 1973, and 5 in 1974. Culturing will be continued indefinitely on a semiannual basis. Also, selected kids will be hand-reared from birth, away from other goats, and used to establish the nucleus for a Johne's-free herd.

Brucellosis testing is performed annually in the canine breeding colony swine and goat herds and in the sheep flock. All new acquisitions are tested during the quarantine period. No new cases were observed.

Hernias, prolapses, hindquarter weakness, and cardiovascular problems occurred with regularity among members of an inbred line of NCI miniature swine. Because the value of these pigs is dependent upon their inbred condition, clinical therapy, surgery, and supportive nutrition were provided to each animal as required on a continuing basis.

Pneumonia continues to be a major problem in young, lab-reared dogs. Possible inadequacies of artificial heat sources during the early neonatal period and indications the nutrition of older pups is less than optimal are being investigated.

The occurrence of respiratory disease in dogs immediately prior to issuing them to investigators required remedial measures. Correction of housing and husbandry procedures at the contract source of dogs and revision of distemper immunization schedules for lab-reared dogs produced at the Animal Center resolved the problem.

The incidence of tuberculosis among large, imported rhesus monkeys increased significantly to 5.5 percent. Because most animals reacted to tuberculin tests late in the routine quarantine period, it was necessary to extend the period of quarantine substantially. Radiography also was used as a diagnostic ally. The reason for the increased incidence of this disease was not determined.

2. Comparative Pathology Section

The Animal Disease Investigation Service answered 290 calls for assistance, an increase of 108 calls, or 59 percent, over the previous year. These involved consultative, diagnostic, and therapeutic activities. Animal species encountered included rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls also varied and involved all Institutes. Supplemental pathology examinations were required in 145 of the investigations, 39 required microbiologic testing, and 24 employed clinical pathology tests. This service continues to be well received by BID investigators and is mutually beneficial to the investigators and VRB professional staff.

A written "VRB Quality Assurance Program for Microbiological Monitoring and Disease Surveillance of Small Animals" was prepared which describes in detail the methods and responsibilities for monitoring rodents. Similar quality assurance programs were described in lesser detail for large animals.

3. Small Animal Section

About 500,000 VRB-produced rodents and rabbits were issued to investigators, which is equivalent to the number produced last year. There was an increased requirement for and production of VRB inbred mice. However, inbred mouse production declined some in the third quarter because of a contamination of the production colonies by Sendai virus. The total demand for VRB strains and stocks of mice was not satisfied because of limitations on current production levels due to personnel ceiling restrictions. Approximate animal issues were as follows:

Inbred mice	250,000
Noninbred mice	165,000
Inbred rats	10,000
Noninbred rats	20,000
Inbred guinea pigs	14,500
Noninbred guinea pigs	11,000
Hamsters	4,500
Rabbits	1,500
Germfree rats	300
Germfree mice	350

The Frederick Cancer Research Center (FCRC) continued to rely on VRB foundation colonies as the genetic base for their rodent colonies. Pedigreed mouse and rat strains were supplied from VRB barrier-maintained colonies. Preparations have been made to supply them germfree pedigreed stock for four inbred mouse strains and one inbred rat strain. VRB has assumed the responsibility of maintaining the genetic base for a variety of other NCI contract programs requiring germfree pedigreed stock and breeding nuclei of mice provided to several NCI contractors. This is the first year DCT (NCI) has used this service.

The 14G barrier facility was improved with the addition of a new, pass-through, high vacuum autoclave. Installation of the autoclave required making floor-to-ceiling holes in the walls to the building and the barrier. This was accomplished without contamination to the barrier. However, a chilled water line in the barrier burst, flooding several rooms. Following this, Pseudomonas aeruginosa was recovered from the guinea pigs, but no other contamination resulted.

Efforts to develop acceptable pathogen-free rabbits continued. VRB strains were hysterectomy derived and foster nursed in a clean conventional area by pathogen-free stock provided by Edgewood Arsenal. The rabbits remain free of the usual pathogenic organisms, including Bordatella and Pasteurella; however, mortality is excessive from nonspecific gastrointestinal problems. "Pathogen-free" rabbits were received from other sources with the hope that their gastrointestinal flora would eliminate the enteric problem. Only one source had rabbits that tested pathogen-free and were able to be exposed to the NIH rabbits. Efforts continued to develop pathogen-free guinea pig colonies in the barrier and in F wing. Both colonies are now producing.

Production colonies of rats in F-wing are now on automatic watering (Systems Engineering and Edstrom) devices which are working satisfactorily. All breeding rats are now housed in new 8" deep, filtered, plastic cages replacing the 6" cages previously used.

Hybrid matings involving three inbred mouse strains indicated some genetic contamination of the production colonies because of unexpected coat colors in the offspring. Extensive testing of the genetic integrity of production, pedigreed-expansion, and foundation colonies was performed by test mating, skin grafting, mixed lymphocyte culture and biochemical methods. Tests indicated there was no contamination of any of the foundation colonies.

The production colonies of BALB/c mice and the pedigreed expansion colonies of A/HeN and AKR/N mice were compromised. These colonies were eliminated and reestablished from the foundation colonies.

The total purchase of rodents and rabbits from contractors increased from 84,000 in FY 1975 to approximately 150,000 this year.

New VRB contracts were established this year for Hartley guinea pigs from Dutchland, Inc.; inbred mice from The Jackson Laboratory; and mice and rats from Microbiological Associates, Inc. A delivery service arrangement was developed from National Airport to NIH investigators' laboratories. Pickups of contract animals are made by a local firm. An itemized list of animals purchased on contract is as follows:

Rabbits--Dutchland and Bar Harbor	7,000
Sprague Dawley Rats--Taconic	28,000
Hamsters--Lakeview	7,500
Swiss Mice--Taconic	28,000
Rats--Charles River	8,500
Rats--Microbiological Assoc.	19,000
Mice-- Microbiological Assoc.	9,000
Mice--Jackson Laboratory	40,000
Hartley Guinea Pigs--Dutchland	2,000

In addition to supplying animals for intramural investigators, breeding nuclei from these colonies serve as a resource for the international biomedical research community as many of the stocks, strains, and substrains are not available elsewhere. The World Health Organization has designated VRB an International Collaborating Center for this activity.

About 350 investigators were provided with litters of inbred animals to start colonies. This was more than in previous years. Also, several hundred noninbred animals were provided as breeding stock. Several commercial producers also were provided with breeding stock. Requests were particularly numerous for the rats with diabetes insipidus and hypertension, nude mice, and inbred NZB, NZW, and CBA/N mouse strains.

The section continued to assist investigators in obtaining new animal models to meet previously unfilled research needs. In some instances, new strains of existing laboratory animals exhibiting unique physiological or anatomical characteristics were used. In others, animals having characteristics required in a particular research problem were adapted from nature. New models are hysterectomy derived and foster nursed or hand nursed prior to introduction into the NIH colonies. Eight new strains were added to the repository at the request of NIH investigators. They are:

Mice	Rats	Guinea Pigs
FVB/N	LOU/MN	R9/LacN
SPM/N	Incisorless (Inc)	OM3/LacN
WB/ReN-W^v/+		B/LacN

At the recommendation of a National Research Council committee studying the repository, the following strains were deleted:

MICE Inbred	RATS Outbred		HAMSTERS Outbred
CBAfb/LwN	NIH Black rat	N:BLK	"Albino"
I/AnN	Japanese rat	N:JPN	

Mutant	RICE RAT
Brachypodism (BALB/cAnN-bp	
Lens rupture (lr)	
Piebald (C3H/HeN-s)	
Syndactylism (BALB/cAnN-sm)	
Tailless (BALB/cAnN-t^n)	
Yellow (AY)	

No problems have been reported from use of the VRB-developed open formula laboratory animal rations. They are used throughout the research community as well as at NIH. All animal colonies maintained by the section are being fed open formula rations except inbred guinea pigs. An autoclavable ration containing 18 percent crude protein is now being fed to barrier-maintained rat and mouse colonies. This product replaces a commercial ration containing 24 percent crude protein, which costs 25 percent more. The cost of maintaining the barrier rat and mouse colonies at current levels should decrease by approximately $25,000 per year.

Contract monitoring of animal feeds for nutrient concentrations indicate that NIH feeds are generally in compliance with specifications. High ash concentrations were reported in several samples of dry dog food. The feed contractor was advised to alter the formula.

Analyses of random samples of animal feeds for various contaminants indicated lead concentrations are increasing and may be a potential problem in animal colonies. Routine assays for lead are to be performed on all NIH animal feed.

Twenty special experimental open formula rations were formulated for specific research projects. Nine of the rations were for NIH investigators and eleven were for investigators from other government agencies or universities.

Studies were initiated to evaluate an open formula ungulate ration at the Animal Center; to determine the effect of varying concentrations of dietary crude fat on hypertension in four strains of inbred rats; to determine nutrient requirements of mice reared in SPF environments; to identify possible nutrient deficiencies in rations for SPF rabbits; and to determine the stability of various forms of ascorbic acid in guinea pig feeds. One of the animal contractors has expressed an interest in using open formula feeds in mouse and rat breeding colonies producing animals for NIH. Experiments have been proposed to evaluate these rations in the contractor's animal facilities.

Data accumulated during a study conducted in SPF mouse colonies indicate there is no antimetabolite activity that affects mouse reproduction as a result of autoclaving rations with high thiamin concentrations.

4. Veterinary Medicine and Surgery Section

The surgical facilities are primarily available for the use of BID investigators; however, surgery frequently is performed by staff veterinarians assigned to the section in support of BID programs in the development of surgical animal models. In addition, staff veterinarians provide surgical and clinical veterinary care to laboratory animals as an essential part of their responsibility to assure optimal health of these government-owned animals. Assistance to BID investigators is provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals. A 500-milliamperage radiographic unit with fluoroscopy is available for research animal services. The number of surgical procedures was approximately 850 this year, an increase of about 10 percent. This was achieved with the relocation of the Surgery Unit from Building 28 to Building 14E. This new location permits more surgical and support space for increased numbers and types of procedures.

Experimental surgical procedures continue to be complex protocols with numerous thoracic, cardiovascular, and abdominal procedures which demand a high level of technical support. More professional and technical assistance to the BID investigators was made possible during the year with an increase in staff and facilities.

The timed pregnant rhesus monkey breeding colony was reduced from 140 to 60 female breeders. Male and new breeders represent an additional 30 animals in this colony. The reduction was necessary to meet NIH requirements for establishing contract breeding colonies of rhesus monkeys. An extensive renovation of the facilities also caused a reduction in the in-house breeding colony. The VRB in-house colony will be gradually increased with breeder female cynomolgus monkeys. These primates are closely related to the rhesus monkey. During the past year, a total of 64 timed pregnant animals were issued from the in-house VRB colony. A new 3-year contract was implemented to provide an additional 100 timed pregnant rhesus monkeys per year. The availability of these timed pregnant rhesus monkeys for intramural investigators will become an increasingly significant asset as the import supplies of rhesus monkeys dwindle.

A total of 39 timed pregnant baboons were issued to investigators through VRB contracts. The current supply of timed pregnant baboons is meeting the total intramural needs.

Renovation of Building 14D was started and scheduled for completion in the fall of 1976. This renovation is a joint program between DRS and the Bureau of Biologics (BOB) and will provide a centralized primate research holding facility. It is designed to permit infectious disease studies, provide a working environment for personnel, and minimize cross infection. When completed, the total capacity of the facility, including prior renovations, will make it the largest primate research facility in the country with a maximum population of over 1,800 animals.

The research holding program of Building 28 has increased in scope with greater diversity of species--dogs, cats, miniature swine, goats, sheep, and other large laboratory animals. Included are new collaborative VRB research programs with NCI and NHLI. The long-term atherogenic diet study in dogs in Building 14E will relocate to Building 28 as time and space permit. A large-scale atherosclerosis research study with NHLI, using miniature swine, has required extensive husbandry, professional, and technical collaboration and support from this unit.

The population of research animals in the facility averages approximately 380 a month. In addition, research animals requiring only infrequent investigator manipulation are maintained on control. This has permitted a less dense animal population per kennel and allowed better animal care practices. Renovations of the indoor-outdoor research animal holding facilities are scheduled for this fiscal year.

D. Problems

1. Animal Center Section

Availability of quality, blood group CEA 1, 2, and 3 negative, microfilaria negative, dysplasia-free dogs as additions to the breeding colony continued to be extremely limited. Rigid selection requirements will continue to retard the full development of the breeding colony. The fact that many bitches are becoming aged compounds the problem of attaining a maximally productive colony, because they also must be replaced.

A 15 percent decline in NIH use of dogs poses a dilemma because it cannot be ascertained whether this is a permanent reduction. Thus, it is difficult to formulate management plans for future canine activities.

The sheep flock (donors and stock animals) was restricted from expanding to meet overall BID requirements because of delays encountered in putting the leased property into operation. A need remains for NIHAC to provide short-term housing for a substantial number of sheep coming from or returning to the NHLI contractor and Bethesda.

While the supply of rhesus monkeys from India remained constant during the first 7 months, deliveries ceased during February and March because of quota restrictions imposed by the Indian government. During that period, small monkeys were issued exclusively to the Bureau of Biologics, and large monkeys were reserved for contract breeding programs. The unexpected need to replace many breeders at Perrine, coupled with a high (5.5 percent) incidence of tuberculosis among large monkeys late in quarantine, delayed satisfying contractor requirements for breeding stock until late in the year.

Contract prices for several animals and products increased. The cost of purebred foxhounds increased by 6 percent and the purchase price for monkeys increased by 10-18 precent (estimate). The escalation was attributable to inflation and improved shipping standards for monkeys imposed on contractors.

2. Comparative Pathology Section

The most serious disease problem during the year was Sendai virus infection of C-wing (conventional colony) mice. The disease was first noticed as mild morbidity in young BALB/c mice in a stock room. Autopsies revealed patchy pneumonia and serologic tests demonstrated Sendai virus-antibody. An initial survey of the wing located the disease in two production rooms and, soon afterward, in all rooms. The plan to eradicate the disease was to sacrifice the mice, decontaminate the wing, and repopulate with mice from F and G wings (barrier colonies). The source of the infection was not determined. The danger of infection with this and other agents is high in C-wing, which is not protected by "barrier" system. Barrier facilities for all NIH rodent colonies are planned within the next several years.

Cecitis in C-wing rabbits continued to be a major problem, resulting in 471 deaths. Monthly mortality varied considerably, correlating roughly with the population of young rabbits at risk. Although the highest mortality is in 6- to 10-week old rabbits, the disease may occur at any age. Bacteriologic studies indicate that the disease may be caused by imbalances of intestinal microflora. The microflora often changes from predominantly gram-positive to gram-negative bacteria of several genera. Overgrowth of bacteria, however, has not been consistently shown. Although the most severe problems with cecitis have followed the widespread use of antibiotics, the disease continues in the absence of antibiotic treatments.

Scurvy was diagnosed in guinea pigs in the 14G barrier colony. Two animals died with typical bone and hemorrhagic lesions of scurvy with were confirmed microscopically. In several months preceding these deaths, approximately 25 animals died of various intestinal problems, which retrospectively appeared to have been scorbutic enteropathy. Investigations indicated that the animals' feed was deficient in Vitamin C as a result of prolonged storage. The disease disappeared soon after supplemental vitamin C was provided in the drinking water.

An outbreak of tuberculosis occurred in a room of pigtail macaque monkeys in Building 14D. Investigations indicated that introduction of an "anergic" animal caused the outbreak. Five monkeys were affected, and all were caged adjacent to or near the anergic one. The disease was eliminated by weekly tuberculin testing and sacrificing the reactors. Mycobacterium tuberculosis was cultured from the lesions.

A large number of guinea pigs died in the B-wing foundation colonies soon after they were dusted with lindane to combat ectoparasites. Fifty percent of the 72 fatalities occurred within 3-8 days after the dusting. Animals of all ages were affected. The findings of pulmonary congestion and hemorrhage and gastrointestinal hemorrhage were consistent with lindane toxicity. CNS disturbance, which occurs in most species, was not observed. After dusting was discontinued, mortality decreased to normal low levels.

After the six barrier rooms in Building 14G were flooded by a broken water pipe, bacteriologic monitoring revealed contamination of rats in one room by Pseudomonas aeruginosa and increased numbers of staphylococci. Fortunately, Pseudomonas disappeared from the room in less than a month.

Investigations were conducted which point to wild rabbit feces as a possible source of contamination of animal feeds with the spores of Bacillus piliformis. Cottontail rabbits were found to be highly susceptible to this agent, which causes Tyzzer's disease in a wide variety of laboratory animals as well as horse foals. Wild rabbit blood contributed by hunters in northwestern Maryland was found to contain complement fixing antibodies to B. piliformis. The results of these studies suggest also that Tyzzer's disease may be the cause of major die-offs of rabbits in the wild.

Johne's disease was found in five goats, the same number as in the previous year. The disease is considered difficult to eradicate since the causative organism is relatively stable in the environment and its detection in animals incubating the disease is laborious. Goats may incubate the disease for several years before fecal cultures reveal the causative agent. Current information indicates that Johne's disease is endemic in Maryland and that anyone buying goats on the open market will, in time, purchase animals with the disease.

Canine distemper was diagnosed histologically in several litters of foxhound puppies. Random source dogs were believed to be the source of infection.

Filaroides sp. was determined as the etiology of verminous pneumonia in foxhounds purchased from a contractor in Kansas in the early fall of 1975. No cases have been recognized since that time which may coincide with the onset of inclement weather and seasonal elimination of the intermediate host.

An outbreak of bordetella pneumonia occurred in the genetic colonies of Strains 2 and 13 guinea pigs. The outbreak was stopped by use of the Bordetella bronchiseptica vaccine which was developed in 1964 and used since then to prevent pneumonia in the Strain 13 production colonies. After the current outbreak, the decision was made to vaccinate the breeders of all strains and stocks of guinea pigs. Bordetella pneumonia never has been observed in properly vaccinated guinea pigs.

The monkey breeding facility at Perrine, Florida, experienced an outbreak of a progressive debilitating disease which was finally shown to be caused by exposure to polychlorinated biphenyls (PCB's). Gas chromatographic analysis of tissues from affected monkeys and samples of concrete from monkey runs revealed similar PCB compounds. The concrete sealer, which also contained PCB's was suspected to be the source. The surface of the concrete runs in some areas contained PCB levels up to 5,000 ppm. Two ppm in the feed of rhesus monkeys has been shown to be highly toxic. Recent resurfacing of the runs appears to be preventing new toxic exposures.

Acute myocardial necrosis and hemorrhage was diagnosed in two swine on an atherosclerosis study. The lesions were typical of those produced by vitamin E-selenium deficiency in swine. Further inquiry revealed that these animals were on a high unsaturated fat diet without adequate vitamin E supplementation, which predisposed them to the disease.

Several membranous glomerulonephritis was found in three squirrel monkeys that died while undergoing neurologic studies. This disease is recognized as a common condition of the squirrel monkey in several primate research centers, but has not been a problem at NIH. It is suspected that the renal lesion is caused by the coating of glomerular membranes with circulating antigen-antibody complexes. A causative antigen has not been identified.

A tuberculosis outbreak occurred in rhesus monkeys in a laboratory that introduced monkeys from several outside sources without subjecting them to quarantine in accordance with NIH policy. The disease was eliminated by sacrificing two monkeys with positive tuberculin reactions as well as six that were exposed to the reactors. Mycobacterium tuberculosis was cultured from the pulmonary lesions of one of the reactors. Six human contacts and twenty-six persons possibly exposed were placed under medical surveillance.

Systemic fat embolism caused the death of three squirrel monkeys in a laboratory performing neurologic surgery. Probable causes of the problem were identified and the surgical technique was altered with corrective results.

An outbreak of pneumonia resulting in debilitation and death of rats in a laboratory colony in one of the Institutes was found to be caused by Streptococcus pneumoniae. Antibiotic sensitivities were determined and treatment instituted to permit completion of ongoing studies. It is expected that the animals eventually will have to be sacrificed since the agent is extremely difficult to eliminate from rat colonies.

No large-scale epizootics occurred in the BIDs this year. Examples of lesser problems encountered are as follows:

Klebsiella pneumoniae infection caused the death of a large number of mice in a population-behavior study in one of the Institutes. The mice died of splenic, hepatic, and pulmonary abscesses from which K. pneumoniae was consistently isolated. Since infrequent change of bedding was a built-in feature of the experimental protocol, the environment of these animals was optimal for this type of epizootic.

3. Small Animal Section

It now appears that the program initiated in 1968 to hysterectomy derive foundation colonies for all mouse and rat strains and stocks may not result, as expected, in the issuance of strictly pathogen-free animals to investigators. Although VRB barrier colonies remain uncontaminated for periods beyond expectation, the production colonies in conventional facilities were reinfested with internal and external parasites and infected with certain viruses. Whether this was due to inadequate decontamination of facilities or a recontamination by a resident feral rodent population in the Building 14-28 complex is undetermined. Perhaps the design, construction, location, state of repair, and age of the buildings housing the present rodent colonies make it unrealistic to expect maintenance of a totally pathogen-free status of rodents following hysterectomy derivation. The facilities for rodent production are not barriers and are in close proximity to quarters for primates, sheep, and carnivores. Nonetheless, the effort to produce pathogen-free rodents will continue, and a systematic plan for improving the facilities for rodent production has been developed.

Most General Schedule (GS) biological laboratory technicians working in the barrier are being paid less than Wage Grade (WG) animal caretakers in conventional colonies performing less technically skilled work. The conversion of these employees to GS pay scale has worked to their disadvantage because of large WG pay increases. GS technicians in the gnotobiotics unit and professional services staff, as well as the barrier, are inadequately compensated compared to WG employees. Unless the situation is corrected, recruitment of qualified employees into these areas will become impossible and the opportunity for upward mobility from SAS caretakers to technicians will become nonexistent. Employees presently assigned these jobs are becoming interested in leaving or returning to WG animal caretaker positions. Plans to create additional barrier space, which will require more technical support, will not be feasible until the inequity is corrected.

3. Veterinary Medicine and Surgery Section

Extensive renovations are scheduled for Building 14E. This will permit full expansion of the VRB experimental surgery program and will accommodate the NHLI experimental surgery activities now in Building 3. During the renovation period there will be considerable interruption of surgical programs to allow the contractors to work in the area. The Comparative Medicine Unit also requires renovations in several indoor animal wards. Until these renovations have been completed, there will be insufficient space for holding immunosuppressed animals or other animals requiring intensive care. The extensive renovations to Building 14D will continue to cause some hardships on the primate research program. Primates will be moved about, shipped to contractors, or other arrangements made to permit contractor access to the facility. Interruption in heating, ventilation, lighting, and water may cause temporary impediments to ongoing research projects.

D. Program Plans

1. Animal Center Section

The canine socialization program which was formally initiated this year will be further refined for continuing application to colony-reared dogs.

Continued expansion of the canine breeding colony by purchase of quality dogs from outside sources will be pursued. Contract production of purebred foxhound puppies (approximately 500/year) will be continued. Creation of outdoor housing space for growing puppies is expected to be completed early in the year. This program will permit purebred production to expand by 200-300 pups per year.

The dairy goat and burro breeding herds will be expanded. About 15 jennies were bred in FY 1976 and are expected to foal in the spring of FY 1977.

Health surveillance of ungulate herds and flocks will be expanded and intensified. Emphasis will be placed on identification and containment of equine diseases because of implementation of a burro breeding program.

Contractor primate breeders will be supplied with replacement rhesus breeding stock on a continuing basis. The Animal Center program will be readjusted in order to provide holding space for young monkeys produced by contractors. These are expected to be available in small numbers initially.

Improvement of leased property consisting of some 200 acres of pasture and several buildings adjacent to the Animal Center will provide space for programs using sheep, swine, and burros. Complete renovation of a pole barn will permit expansion of sheep activities (200-550 head). Expansion of swine breeding/holding activities is anticipated early in FY 1977 with the erection of a temporary farrowing/holding structure.

2. Comparative Pathology Section

A new program of animal genetic monitoring will be initiated in collaboration with the Small Animal Section. The program will be concerned with developing animal characteristic profiles and monitoring for genetic contamination of animal strains through the use of biochemical marker and gene mapping.

3. Small Animal Section

An 8-year plan for renovation of the rodent production buildings has been developed. If approved, Building 14F and 14C will be converted into barriers and the 14G barrier will be revitalized. A portion of Building 14E will be isolated for use by the professional staff; an isolation facility for microbiologically contaminated animals is to be provided in a section of Building 14B. The remainder of Building 14B will be improved as a conventional facility.

A computerized recordkeeping system is being developed by VRB personnel and DRS management analysts with the assistance of personnel from the National Center for Toxicological Research, FDA. Primary emphasis is on collection of data on rodent breeding performance. Mating and mortality data will also be collected.

An expanded program of genetic monitoring is planned to provide adequate safeguards for the integrity of inbred strains. A routine testing program involving test matings, histocompatability testing, mandible analysis, and biochemical tests will be established as a collaborative effort with the Comparative Pathology Section.

Present obsolete cages for rabbits and guinea pigs will be replaced as soon as funding is available and an acceptable design is tested. The evaluation of a semiautomated cage for rabbits continues and plastic cages for guinea pig harems are being tested.

A disease surveillance program for the small animal colonies has been developed by a Quality Assurance Committee to ensure prompt detection of disease through SAS and CPS cooperative monitoring. The effort to free all rodent strains and stocks of disease through hysterectomy derivation will continue. Methods will be developed for applying this practice to guinea pigs and rabbits. This requires a cooperative effort in areas of nutrition, microbiology, and genetics.

A survey will be made of investigator requirements for rodents beyond the capability of inhouse production; new contracts to meet these needs will be initiated where possible. Contract efforts will concentrate on developing new breeders with VRB strains serving as the genetic base, i.e., pedigreed breeding stock will be supplied by VRB. In the coming year, contracts are planned for inbred mice and inbred guinea pigs, with contracts for NIH rats and outbred mice being negotiated the following year.

Studies to define the major nutrient requirements of different species and strains of inbred rodents will continue. Efforts will continue to develop open formula rations purchasable through advertised contracts to replace closed formula rations purchased through negotiated, sole source contracts.

4. Veterinary Medicine and Surgery Section

All three units expect increased collaborative research and research support activities during the coming year. In addition, each unit will be involved in major renovations and/or architectural planning. The forecast is for a major expansion of each unit. The Surgery Unit renovation and expansion of facilities in Building 14E will include the surgical activities of NHLI currently in Building 3. This combined activity will essentially centralize all NIH experimental surgery of large laboratory animals in one facility, providing efficient use of space, equipment, supplies, and support personnel. By attracting other BID surgical research, it in turn will allow reassignment of these smaller surgical areas across campus to other BID research functions.

The Comparative Medicine Unit in Building 28 will expand its preoperative and postoperative care to support the Surgery Unit relocation in Building 14E. The

Comparative Medicine Unit, after further renovations, will be better suited for those BID studies dependent upon precise environmental controls. The Primate Research Unit expansion into a large primate research facility with infectious disease study capabilities will give BID investigators a research resource not previously available. The research services of the section are unique and vital to many BID intramural efforts. Each unit activity engages current intramural laboratory animal research in comparative medicine and surgery. Available contract services complement each program but cannot replace the on-campus research support needed by intramural scientists. The future growth of these activities will require the construction of a proposed multilevel centralized laboratory animal facility for the NIH campus and additional personnel ceilings.

F. Publications

Bacher, J.D. and Potkay, S. Compression plating of radial and ulnar fractures in the Goat. *Vet. Rec.* 96: 538-539, 1975.

Clarke, G.L. and Osburn, B.I. Border disease-like syndrome in California lambs. *Amer. Assoc. Vet. Lab. Diag.*, 18th Ann. Proc., 303-325, 1975.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00001-06 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Genetics and Animal Models

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C. T. Hansen Geneticist VRB DRS

COOPERATING UNITS (if any)
Laboratory of Molecular Genetics, NICHD
Laboratory of Immunology, NIAID
Dermatology Branch, NCI
Laboratory of Vision Research, NEI
Divison of Becterial Products, BoB
Arthritis and Rheumatism Branch, NIAMDD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

SUMMARY OF WORK (200 words or less - underline keywords)

The primary thrust of this project is developing new and further defining those animal models already available. The techniques involved include standard mating systems coupled with technological definition as required by each model. Results thus far have been to define the histocompatability (Ag-B) and red-cell (Ag-C) antigens in 18 inbred strains and mutant stocks in the rat. Studies with the nude (athymic) mouse revealed the placental and maternal transfer of thymic activity. The program continues to establish the nude (athymic) gene into 19 inbred mouse strains. Six of the 19 strains have now reached the minimum level of congenicity, i.e., six cycles of outcrossing and backcrossing have been completed.

1. Project Description

Objectives: To study the genetics of naturally occurring variation in animals for the purpose of developing new as well as further defining those animal models presently available.

Methods Employed: The procedures used in these studies involve a combination of direct as well as collaborative efforts. The common element is the underlying genetics but since each characteristic studied requires unique technology, collaborative efforts with respect to technology have been found to be effective.

Major Findings: These include establishing the histocompatability (Ag-B) and red cell (Ag-C) antigens in 18 inbred and mutant strains/stocks of rats for the first time. A study undertaken to determine the cause of skin blisters in the Vibrissaeless (vb) rat indicated that they were the result of intraepidermal separation which was suprabasilar in position.

The development and characterization of the nude (athymic) mouse continues. It has been determined that homozygote X homozygote matings are feasible with the result that this will minimize the problem of possible maternal transfer of thymic activity which should provide a more precise model for studies with this animal. The program to develop congenic strains using the nude mouse with 19 inbred mouse strains continues. Two strains have reached the theoretical level of congenicity with their partner inbred strians and four additional strains have reached a minimum level of congenicity. Also, observations of what first appeared to be a thymus in homozygotes was later found to be lobulated lymph nodes by immunological testing.

Significance: The results from this and other studies provide basic information required for further detailed experiments necessary to understand basic life processes.

Proposed Course: Continuation.

2. Publications

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00002-05 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	J.J. Knapka	Nutritionist	VRB, DRS
Other:	K.P. Smith	Geneticist	VRB, DRS
	F.J. Judge	Supr.Vet.Med. Officer	VRB, DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

SUMMARY OF WORK (200 words or less - underline keywords)

A laboratory animal nutritional research program is being conducted with various strains and stocks of small animals maintained in conventional and specific pathogen-free environments. The primary objectives of the program are to develop and evaluate open formula rations that can be used to improve the nutritional status of animal colonies and to identify differences in nutrient requirements among various strains and stocks of animls. A series of factorial-designed feeding trials are conducted to determine the effect of varying concentrations of dietary crude protein, crude fat, crude rats, guinea pigs, and rabbits.

PHS-6040
(12-75)

1. Project Description

Objectives: To improve the nutritional status of NIH production colonies of laboratory animals by identifying the quantitative nutrient requirements of specific stocks and strains of animals and then providing open formula rations that contain these nutrient concentrations. To identify possible differences in nutrient requirements between animals maintained in conventional and specific pathogen-free environments. To provide NIH investigators with open formula rations to accommodate specific research projects.

Methods Employed: A series of factorial designed feeding trials are conducted to determine the effect of varying dietary concentrations of crude protein, crude fat, crude fiber, and minerals and vitamins on growth and reproduction in mice, rats, guinea pigs and rabbits maintained in conventional and specific pathogen-free environements. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, mortality, weight of offspring weaned, and the postweaning growth of offspring. Studies are also being conducted to determine the digestibility of nutrients in experimental rations and the whole body nutrient composition of various species of small laboratory animals. Data from all studies are coded for computer analyses by the appropriate statistical methods.

Major Findings: Data collected in a large number of production colonies of specific pathogen-free rats and mice indicate many stocks and strains of these species can be maintained on rations containing 18 percent instead of 24 percent crude protein without any significant change in reproductive performance of breeding or preweanling growth of offspring.

Data from studies designed to detect antimetabolite activity as a result of autoclaving rations containing high concentrations of thiamin indicate no compounds with such activity are formed that would affect reproduction in at least two generations of mice.

Special rations have been developed for studies designed to determine the effect of various kinds of dietary fat and cholesterol on the distribution of atherosclerosis in dogs and miniature swine. Preliminary results from these studies indicate the ingredients used in rations for this kind of research can have a profound effect on the course of the disease.

Significance: The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved when rations can be developed that supply nutrients in concentrations nearly equal to the requirements of the animal strain involved. Open formula rations formulated for specific research projects, or for standard rations, provide NIH investigators and the scientific community with an essential research tool when experimental data is to be verified by repeating experiments.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00004-15 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	J.R. Ganaway	Veterinary Microbiologist	CPS VRB DRS
OTHER:	R.S. McReynolds	Microbiologist	CPS VRB DRS
	A.M. Allen	Chief, Comp. Path. Sect.	CPS VRB DRS
	G.L. Clarke	Veterinary Pathologist	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Sectinn

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.7	0.7	1.0

SUMMARY OF WORK (200 words or less - underline keywords)

A continuing purpose of this project is the study of Tyzzer's disease. The topics of present interest are: 1) characterization of the causative agent, Bacillus piliformis; 2) the serological response of the host to B. piliformis infection using the complement fixation test and fluorescent-antibody techniques; 3) the relationship of isolants from the rabbit and horse foal; 4) the pathogenesis of Tyzzer's disease in a variety of laboratory animals; 5) the stability of the spores of B. piliformis under a variety of conditions including temperature variation and contact with chemicals; and 6) the epidemiology of Tyzzer's disease with a view toward determining primary sources of infection in nature.

1. Project Description

Objectives: To characterize the etiologic agent. To study the pathogenesis of the disease through experimental transmission studies. To develop serologic techniques for detection of antibody. To develop a means to control and/or prevent the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: Biological characterization and comparison of isolants from the rabbit and horse foal continues. A one-way cross was observed using the complement fixation test. Results of serological survey indicate that Tyzzer's disease occurs in wild cottontail rabbits in Maryland.

Significance: Within the past decade, this disease has been diagnosed for the first time in nine different species of animals including rats, hamsters, gerbils, rabbits, cats, muskrats, wild hares, nonhuman primates, and horses. The natural history of this disease remains unknown. The etiologic agent, a gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. This disease occurs throughout the world, causes fatal epizootics in a wide variety of species, and is one of the more important diseases of laboratory animals which interferes with and complicates biomedical research.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00007-02 VR

PERIOD COVERED

July 1, 1976 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Environmental Toxicosis of Rhesus Monkeys--Perrine Primate Facility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	G.L. Clarke	Veterinary Pathologist	CPS VRB DRS
OTHER:	A.E. New	Asst. Chief, VRB	VRB DRS
	N. Altman	Perrine Prim. Res. Ctr.	

COOPERATING UNITS (if any)

Perrine Primate Research Center
Perrine, Florida

LAB/BRANCH

Veterinary Resources Branch

SECTION

Comparative Pathology Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

SUMMARY OF WORK (200 words or less - underline keywords)

Tissues were collected from ailing monkeys and submitted to two separate laboratories for analysis. Polychlorinated biphenyls (PCB's) were suspected based on clinical and pathologic observations. This was confirmed using gas chromatography and mass spectographic techniques. The source of PCB's was a concrete sealer used on the outdoor runs. The surface of the runs has been coated with polyurethane, and the problems related to PCB toxicosis have abated. The overall health of the colony appears to have greatly improved.

Project Description

Objectives: To determine the cause of progressive debilitation and death among the rhesus monkeys housed at the Perrine, Florida, facility.

Methods Employed: The problem is being studied by histopathological, clinical, pathological, and epidemiological means. The history and pathology is suggestive of a toxicosis produced by exposure to polychlorinated biphenyls (PCB). Tissues and materials suspected of containing these compounds are being analyzed by gas chromatographic and mass spectrophotometer methods.

Major Findings: PCB's are present in the tissues of exposed primates in toxic levels. This has been confirmed by two separate laboratories. PCB's are also present in the concrete of the outdoor primate runs.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00008-02 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Neoplasia in the Nude Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.L. Clarke	Veterinary Pathologist	CPS VRB DRS
OTHER:	C.T. Hansen	Head, Genetics Unit	SAS VRB DRS

COOPERATING UNITS (if any)
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.2	OTHER: 0.1

SUMMARY OF WORK (200 words or less - underline keywords)

Tumors involving many organ systems have been collected to date. These are presently being classified histologically. This information is being correlated with nude mouse production figures to determine incidence of neoplasia in the nude mouse.

PHS-6040
(12-75)

Project Description

Objectives: To determine the prevalence and types of neoplasia that occur in this inbred strain which is genetically deficient in cell mediated immunity.

Methods Employed: Retired females are maintained behind the barrier at Building 14G for aging and sent to the Comparative Pathology Section when they show any signs of abnormality. Males are sent to the Section following retirement and are maintained in relative isolation in the Horsfall units and killed when they exhibit any abnormal signs.

Major Findings: There are sketchy reports that claim nude mice have a relatively low rate of neoplasia. Numerous cases involving neoplastic changes have been observed to date, involving many organ systems.

Significance: If nude mice in fact do experience a significant rate of neoplastic disease, this will be a worthwhile contribution to the scientific literature.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00009-03 VR

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Sodium Cyanate Neurotoxicity in Macaca nemastrina primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	David K. Johnson	Chief, VMSS	VRB DRS
	Robert A. Whitney, Jr.	Chief, VRB	DRS
	French Anderson	Molecular Hematology	IR NHLI

COOPERATING UNITS (if any)

Molecular Hematology Branch, Division of Intramural Research, NHLI

LAB/BRANCH

Veterinary Resources Branch

SECTION

Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

SUMMARY OF WORK (200 words or less - underline keywords)

Sodium cyanate, a chemotherapeutic agent for Sickle Cell disease, inhibits irreversibility of the sickling of erythrocytes from patients with this disease by reacting specifically with the NH_2-terminal valine of the hemoglobin molecule without significantly destroying erythrocyte metabolism or function. It has been suggested that sodium cyanate may elicit neuropathology in pigtail monkeys, Macaca nemastrina. The outcome of this study will provide information for development of further clinical studies for use in humans suffering from Sickle Cell disease.

PHS-6040
(12-75)

Project Description

Methods Employed: Twenty adult female pigtail monkeys, Macaca nemastrina, will be divided into four groups; one as a sham control and the other three groups will receive daily subcutaneous injections of sodium cyanate at 40 mg/kg, 25 mg/kg, and 15 mg/kg, respectively. Selected animals will be humanely killed and perfused for neuropathological examination. Clinical neurological examination and clinical laboratory tests will be run routinely during the course of the experiment. Baseline hematology, clinical chemistries, and neurological evaluation have been compiled over 3-month stabilization period.

Major Findings: The 40 mg/kg dosage produced acute toxic effects, primarily anorexia, depression, electrolyte imbalance, cachexia, and death. This dose was reduced to 35 mg/kg which prevented death but was clearly toxic to the primates. The dosage of 25 mg/kg results in mild clinical neuropathies as evidenced by impairment of peripheral neurological reflexes. Depression and cachexia were not observed in the dosage group (25 mg/kg). The 15 mg/kg remained clinically normal, similar to the control group. Approximately half of the animals from each group have been humanely killed for gross and histopathological examination. Special studies in central and peripheral neuropathology are underway, including light and electron microscopy.

Significance: The sodium cyanate reverses the sickling of erythrocytes and results in relief of symptoms of Sickle Cell disease without impairing the oxygen transport system of erythrocytes. Establishing a dose-toxic curve in primates wil lead to implementation of safe clinical dosage curves for human beings suffering from this disease. Sodium cyanate has interest for its in vivo clinical use as well as extracorporeal treatment of affected drythrocytes. This drug has potential for other anemias associated with abnormal hemoglobin caused by genetic, inborn errors of metabolism.

Proposed Course: Continuation of this study to its conclusion to compare short-term and long-term effects of sodium cyanate on peripheral and central nervous system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 00010-03 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Erythrocebus patas Monkey as an Animal Model for Cardiovascular Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	Donald L. Fry	Chief, IR EA	NHLI
OTHER:	Robert W. Mahley	Chief, Sect Comp. Atherosclerosis & Metabolism	NHLI
	David K. Johnson	Chief, VMSS	VRB DRS

COOPERATING UNITS (if any)
Laboratory of Experimental Atherosclerosis, NHLI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the advantages of the patas monkey for atherosclerosis in comparative studies as they relate to human disease.

PHS-6040
(12-75)

Project Description

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for four months while baseline data was obtained. They were randomly divided with equal sex distribution into one group of 10 animals receiving monkey chow, one group of 20 receiving high fat-low cholesterol, and one group of 20 receiving high fat-high cholesterol. Monthly blood samples were drawn and hematological, serum chemistries, and serum lipid profiles were obtained.

Major Findings: The test group receiving high fat-high cholesterol had a rise in serum cholesterol levels which persisten while being fed the atherogenic diet. The serum lipid profiles of the other two groups were similar. After 12 months on the study, one-half of each group was humanely killed and necropsies performed with emphasis placed on the cardiovascular system. Atherosclerosis lesions were evident in the high fat-high cholesterol group. After the end of an additional 12 months, the balance of the animals were humanely killed and necropsied. More severe atherosclerosis was efidenced in the high fat-high cholesterol group, with evidence of some coronary artery disease and a few cases of cholesterol gallstones. The high fat-low cholesterol animals had some indication of mild disease, and detailed histological and histochemical evaluations are now in progress.

Significance: Atherosclerosis is a leading cause of death. Basic research explaining the pathogenesis of this disease on a biochemical, lipid analysis, force dynamics, and formation of atherosclerotic plaques will provide answers to the control of this disease. The patas monkey is emerging as one of the best primate models for human disease.

Proposed Course: A continuation of these studies with emphasis placed on feeding these animals a diet resembling a typical American diet. Similar methodology employing the same controls will be followed so that comparison of these studies can be accomplished.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00011-02 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Effect of Season on Pituitary and Gonodal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.K. Johnson	Chief, VMSS	VRB DRS
OTHER:	G.D. Hodgen	Chief, Endocrinology Sec	RR NICHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1.0

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

Project Description

Methods Employed: Ten male breeder monkeys will be bled the first five days of each month for a twelve-month period. Follicle Stimulating Hormone, Leutinizing Hormone, Testosterone, and Androsternedone will be assayed using the sensitive radioimmunoassay methods. These results will be correlated to time of month, season, and breeding efficiency.

Major Finding: Study is still in progress.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensively studied. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. The direct application of these results is essential to the biomedical research support required for improving nonhuman primate breeding. These large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00012-02 VR

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Hormone Level During the Postpartum Interval in Nursing and Non-nursing Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.K. Johnson	Chief, VMSS	VRB DRS
OTHER:	G.D. Hodgen	Chief, Endocrinology Sec.	RR NICHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHD

LAB/BRANCH

Veterinary Resources Branch

SECTION

Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	0.5	1.5

SUMMARY OF WORK (200 words or less - underline keywords)

The interval from delivery to the first fertile menstrual cycle in rhesus monkeys is not known. Breeding management requires such information to maximize the use of breeder males for space management planning and efficiency in timed-mating protocols. Serum levels of various gonadal hormones will be measured to identify the onset of ovulating menstrual cycles.

PHS-6040
(12-75)

Project Description

Methods Employed: Five nursing rhesus monkey mothers and five non-nursing mothers will be bled for 90 days beginning one day after elivery. Serum levels of Follicle Stimulating Hormone, Leutinizing Hormone, Estradiol, Estrone, and Progesterone will be measured to identify the onset of ovulatory menstrual cycles.

Major Finding: Study still in progress.

Significance: The development of domestic breeding colonies of rhesus monkeys to provide a continued resource fo these animals for biomedical research. Improved understanding of their reproductive physiology leading to improved fertility and management practices are essential. These results provide endocrine parameters for comparative medicine for human health.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00013-02 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Mycoplasma Induced Caprine Keratoconjunctivitis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	E.J. Baas	Head, Carnivore Unit	ACS VRB DRS
OTHER:	M.F. Barile	Director, Mycoplasma Branch	BoB FDA
	R.M. Franklin	Johns Hopkins University	

COOPERATING UNITS (if any)

Wilmar Ophthalmology Institute, Johns Hopkins University
Baltimore, Maryland

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.1	OTHER: 0.2

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine if Mycoplasma conjunctivae is an etiological agent of naturally occurring caprine keratoconjunctivitis (pinkeye). Attempts are being made to experimentally induce the disease and study both forms by bacteriological, serological, pathological and serum chemistry methods.

Project Description

Major Findings: The major findings indicate there are natural cyclic epizootics due to this agent and that while serum antibodies do not increase, local antibody can be detected in the synovial fluid of arthritic joints. Experimental disease can be induced in adult goats, but definite immunity may not be acquired. Presently, more data is required to substantiate previous findings.

Significance: Preventing a herd disease in experimental animals and utilizing the goat as an animal model for Reite's Syndrome in humans.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00014-02 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Evaluation of M. bovis PPD Tuberculin in Feral Macaca Mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.M. Renquist	Head, PQU	VRB DRS
OTHER:	D.W. Johnson	Dept. Vet Clin Science, UM	
	L.D. Konyha	USDA	

COOPERATING UNITS (if any)
Dept. Veterinary Clinical Sciences, U. Minnesota, St. Paul, MI
Animal & Plant Health Inspection Services, USDA, Hyattsville, MD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	0.10	0.05

SUMMARY OF WORK (200 words or less - underline keywords)

The efficacy of Mycobacterium bovis purified protein derivative (PPD) tuberculin is compared to standard veterinary mammalian tuberculin in the early detection of naturally acquired tuberculosis in rhesus monkeys. Progression of disease, hypersensitivity and necropsy is studied in affected animals.

PHS-6040
(12-75)

Project Description

Objectives: To determine the efficacy of Mycobacterium bovis purified protein derivative (PPD) tuberculin as compared to that of the standard veterinary mammalian tuberculin in the early detection of naturally acquired tuberculosis in rhesus monkeys.

Methods Employed: Approximately 50 tuberculous monkeys will be isolated and their comparative skin reactivity to veterinary tuberculin and PPD will be determined. Twelve to twenty tuberculosis-free monkeys will then be paired with tuberculous monkeys. Weekly skin reactions will be measured and photographed and lymphocyte transformation studies performed. On diagnosis of tuberculosis in the conditioned monkey, the pair will be killed and necropsied. Tissue samples will be collected for histopathologic evaluation and Mycobacterium isolation and identification.

Significance: Diagnosis of tuberculosis is a continuing problem in simians. More definitive diagnosis allows early elimination of disease animlas and ultimate usage of simians for research.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00015-02 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Defining the Nude Mouse Model

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	R.A. Whitney, Jr.	Chief, Veterinary Resources Br			DRS
OTHER:	C.T. Hansen	Geneticist, SAS		VRB	DRS
	J.R. Ganaway	Veterinary Microbiologist	CPS	VRB	DRS
	A.M. Allen	Chief, CPS		VRB	DRS
	C.K. Hsu	Johns Hopkins University			
	H.J. Alter	Blood Bank			CC
	P. Holland	Blood Bank			CC
	R. Purcell			LID	NIAID

COOPERATING UNITS (if any)
Laboratory of Infectious Diseases, NIAID
Blood Bank, Clinical Center
Dept. Laboratory Animal Medicine, Johns Hopkins University, Baltimore, MD

LAB/BRANCH
Veterinary Resources Branch

SECTION
N/A

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
-.3	0.2	0.1

SUMMARY OF WORK (200 words or less - underline keywords)

This project is an attempt to further define the role of the nude, athymic mouse as a model for various human disease processes. Initial exposure to the nude mice with human hepatitis A and B virus was unsuccessful. They did, however, demonstrate the role of the cellular immune response in lesions of schistosomiasis. The use of antilymphocyte serum and the breeding of the nude as a congeneic with inbred strains of mice lacking specific immune responses will be continued in an effort to provide a new model for human infectious diseases.

PHS-6040
(12-75)

1. Project Description

Objective: To determine the susceptibility of the nude, athymic mouse to viral, parasitic, and bacterial diseases, and to define the role of the thymus activated "T" lymphocytes in susceptibility and pathogenesis of infectious diseases.

Methods Employed: Weanling nude mice are transferred directly from the Building 14G barrier to presterilized, germfree isolators. Protecting this highly susceptible animal from the conventional environment with the flexible plastic isolator system has proven extremely successful. Many nudes, who have a 4-month life span in conventional animal quarters, survived until sacrificed at 22 months in our isolator system.

This project originated as an attempt to infect nude mice with human hepatitis A and hepatitis B. Serum from a human known to be infected with "B," and from a chimpanzee known to be infected with "A" was injected I.V. into separate groups of animals.

Major Findings: In collaboration with Johns Hopkins University, nude mice in isolators were also exposed to known numbers of infectious Schistosome larvae. After over 12 months of testing for the antigen and antibody for B and for liver enzyme changes associated with A infections, it was concluded that, despite their lack of a cellular immune response, the nude, athymic mouse is not susceptible to human viral hepatitis. In the schistosome work, nudes, while developing heavy infections, do not show the tissue granulomas seen in conventional mice infected with schistosomes. This demonstrates the role of cell mediated immunity in the pathogenecity of this disease.

Significane: This congenital, athymic state, with its resulting lack of cell mediated immunity in the nude mouse, may be one of the most significant events in the evaluation of animal models for human disease. It must be defined in a number of areas to realize its potential and liminations in biomedical research.

Proposed Course: Continuation

2. Publications

Hsu, C.K., Whitney, R.A., Jr., and Hansen, C.T.: Thymus-like lymph node in nude mice. Nature 257: 681-682, 1975.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00016-01 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Characterization of a New Viral Disease of Rabbits

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	J.D. SMall	Animal Disease Investigator, SAS	VRB DRS
OTHER:	R.A. Squire	Head Tumor Path. Section	EPB NCI
	L. Aurelian	Virologist, Johns Hopkins University	
	J.D. Strandberg	Pathologist, Johns Hopkins University	

COOPERATING UNITS (if any)
Johns Hopkins University School of Medicine, Baltimore, MD
Experimental Pathology Branch, NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to isolate and characterize the responsible virus, describe the clinical course, define the lesions, study the mode of transmission, and define the host range. Work so far indicates the agent is a virus. The target tissue is muscle, and the only known susceptible host is the rabbit.

PHS-6040
(12-75)

Project Description

Objectives: To characterize the etiological agent of a hitherto undescribed disease. To study the pathogenesis of the disease.

Methods Employed: Microbiology, immunology, and pathology.

Major Findings: The disease is caused by a virus. It is highly infectious for the rabbit by inoculation but has not yet been naturally transmitted between rabbits. Other species have not been infected. A specific myopathy is associated with the disease.

Significance: This agent may prove useful in the study of myocardial degenerative disease as the agent appears to have a high affinity for myocardial tissue.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00017-01 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
Experimental Atherosclerosis in Miniature Swine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	R.W. Mahley	Head, Comp. Athero. and Arterial Metabolism Section	EA NHLI
OTHER:	D.L. Fry	Chief, Lab. Exper. Athero.	EA NHLI
	R.L. Killens	Head, Comp. Med. Unit, VMSS	VRB DRS
	D.K. Johnson	Chief, VMSS	VRB DRS
	J.J. Knapka	Nutritionist, SAS	VRB DRS

COOPERATING UNITS (if any)
Laboratory of Experimental Atherosclerosis, NHLI
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the effects of different kinds of dietary fats with and without cholesterol on the pathogenesis of atherosclerosis using miniature swine as an animal model for human disease. Experimental atherosclerosis in miniature swine provides a model system for studying the interrelationships of dietary and biochemical factors germaine to the basic causes and mechanism of atherosclerosis.

PHS-6040
(12-75)

Project Description

Methods Employed: Fifty miniature swine from an established biomedical research center were obtained. The animals were of uniform age and size with an equal sex distribution. Following baseline blood chemistry profiles, the animals were divided into the following groups with the following supplements to a defined swine diet: tallow, tallow with 1.5 percent cholesterol; tallow with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; lard, lard with 1.5 percent cholesterol; lard with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; cottonseed oil, cottonseed oil with 1.5 percent cholesterol. The swine were kept on the diet for 6 months and biweekly blood chemistries, and weights were followed. Monthly serum samples were collected for isolation and measurement of specific lipoproteins.

Major Findings: Atherosclerosis was induced in swine fed the cholesterol diets. The degree and extent of the disease correlated with the levels of total serum cholesterol. Significant findings were 1) Thrombosis of the following arteries; basilar, cerebral, anterior descending coronary, posterior descending coronary; 2) human-like atherosclerosis in mid-range serum cholesterol both in distribution and appearance. Histopathology and analyses of all data will be accomplished.

Significance: Detailed investigation of induced atherosclerosis in animal models such as miniature swine is needed to explore the underlying causes and progression of this disease. Atherosclerosis is a major disease of human beings, a leading cause of death, and a debilitating disease affecting all ages. The ability to produce this disease in a reliable, reproducible manner permits the study of a variety of parameters.

Proposed Course: Additional studies will be performed to 1) further examine regression patterns of atherosclerosis, 2) examine thromoplastin and clotting factors as influenced by the course of this disease, and 3) define different dietary factors as to their presence, abscence and level in diet as to induction and influence on atherosclerosis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00018-01 VR

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)
The Pathogenesis of Chondrodysplasia in the Alaskan Malamute

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.M. Young	Lab. of Toxicology		NCI
OTHER:	R.L. Killens	Head, Comp. Med. Unit, VMSS	VRB	DRS
	J.M. Ward	Lab. of Toxicology		NCI
	D. Prieur			NCI

COOPERATING UNITS (if any)
Laboratory of Toxicology, NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

SUMMARY OF WORK (200 words or less - underline keywords)

The Alaskan Malamute has a naturally occurring congenital condition of chondrodysplasia. This is a genetic inborn error of metabolism occurring as a recessive trait with varying degrees of expression. The Alaskan Malamute serves as a useful model for studying the pathogenesis of this disease, especially with growth patterns in puppies. Studies of biochemical, histochemical, and morphological changes serve to define this disease in humans as well as provide mechanisms of pathogenic processes as occur with neoplasms of the skeletal system.

PHS-6040
(12-75)

Project Description

Method Employed: A small colony of approximately ten Alaskan Malamutes have been acquired. This colony has a high incidence of chondrodysplasia in their offspring. The dogs are mated and all offspring are radiographed at routine intervals to detect early change and growth patterns indicative of this disease. Currently, the main emphasis is on repeated breeding and evaluation of bitches and studs, to obtain an increased number of puppies with this condition.

Major Findings: Puppies have been produced with chondrodysplasia. The growth patterns of long bone and epiphyseal development closely resemble the morphological dysplasia as occurs in human beings. Studies employing histochemical analyses and biochemical factors are in progress.

Significance: Understanding the pathological changes in morphological and biochemical parameters of recognized cartilage and bone dysplasia provides mechanisms of action at the cellular level of other disease processes pathological to bone and cartilage. Histochemical, biochemical, and other laboratory techniques can be used for studies of osteosarcomas. Cellular changes in cartilage and bone can be followed, plus improved diagnostic and research techniques can be refined in this animal model system.

Proposed Course: This study will continue in acquiring more Alaskan Malamutes, breeding of F_1 offspring to augment the incidence of the disease, and further cellular, radiographic, and other diagnostic methods will define this congenital defect.

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